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REVIEW ARTICLE

Biomarkers associated with the development of comorbidities in patients with atopic dermatitis: A systematic review

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Abstract

Biomarkers associated with the development of comorbidities in atopic dermatitis (AD) patients have been reported, but have not yet been systematically reviewed. Seven electronic databases were searched, from database inception to September 2021. English language randomized controlled trials, prospective and retrospective cohort, and case–control studies that investigated the association between a biomarker and the development of comorbidities in AD patients were included. Two authors independently screened the records for eligibility, one extracted all data, and critically appraised the quality of studies and risk of bias. Fifty six articles met the inclusion criteria, evaluating 146 candidate biomarkers. The most frequently reported biomarkers were filaggrin mutations and allergen specific-IgE. Promising biomarkers include specific-IgE and/or skin prick tests predicting the development of asthma, and genetic polymorphisms predicting the occurrence of eczema herpeticum. The identified studies and biomarkers were highly heterogeneous, and associated with predominately moderate-to-high risk of bias across multiple domains. Overall, findings were inconsistent. High-quality studies assessing biomarkers associated with the development of comorbidities in people with AD are lacking. Harmonized datasets and independent validation studies are urgently needed.

KEYWORDS
allergic rhinitis, asthma, atopic dermatitis, biomarker, comorbidities

Abbreviations: ACD, allergic contact dermatitis; AD, atopic dermatitis; ADHD, attention-deficit/hyperactivity disorder; AR, allergic rhinoconjunctivitis; BIOMAP, BIOMarkers in Atopic dermatitis and Psoriasis; EH, eczema herpeticum; Eos, eosinophils; FLG, filaggrin; HR, hazard ratio; HSV, herpes simplex virus; IFN-related, interferon-related; IgE, immunoglobulin E; IR, incidence ratio; LOF, loss of function; NR, not reported; NS, not significant; OR, odds ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; PROSPERO, Prospective Register of Systematic Reviews; QUIPS, Quality in Prognostic studies; RCTs, randomized controlled trials; RR, relative risk; s-IgE, allergen-specific IgE; SPT, skin prick test.

Conor Broderick and Stefanie Ziehfreund should be considered joint first author.

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1 | INTRODUCTION

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease, and is increasingly recognized as a lifelong disease affecting around 20% of children and adolescents in high-income countries, and up to 10% of adults.[1–5] AD demonstrates highly variable clinical phenotypes, influenced by poorly understood gene–gene and gene–environment interactions.[6] With its chronicity, complex disease trajectories, and a significant impact on the quality of life of affected individuals and their families, AD is associated with substantial burdens on patients and healthcare resources.[4,7,8] Furthermore, in approximately one-third of individuals affected by AD, there is a well-documented association between AD and the subsequent development of food and respiratory allergies, the so-called "atopic march."[9,10] In addition to asthma, food allergies, and allergic rhinoconjunctivitis (AR), AD has also been associated with non-atopic comorbidities such as allergic contact dermatitis (ACD), neuropsychiatric disorders, infections, malignancy, and cardiovascular diseases.[10]

Given the complexity of AD and the variable response to standard therapies, a shift toward precision medicine rather than using a "one-size-fits-all" approach is of high clinical relevance.[11] The identification of potential biomarkers, providing an objective and measurable indicator of disease activity and response to treatment, has been recognized as a critical step toward person-centered care.[12–15] Validated biomarkers could be used to identify those at risk of disease initiation, disease progression or comorbidity development, and would inform targeted preventative strategies to minimize the burden of long-term disease.[13,14]

In recent decades, several candidate biomarkers related to AD have been proposed. For instance, thymus and activation-regulated chemokine (TARC) has been identified as a biomarker of AD severity,[16] C-C motif chemokine 22 (CCL22) was suggested as a biomarker of response to treatment,[17] and high immunoglobulin-(Ig)E levels and filaggrin (FLG) loss of function (LOF) mutations were proposed as candidate biomarkers for the development of food allergy in patients with AD.[18] However, while these proposed biomarkers are a focus of ongoing research, there are, as yet, no biomarkers approved for clinical use in AD.

BIOMarkers in Atopic dermatitis and Psoriasis (BIOMAP) is a large European consortium aiming to improve our understanding of disease subtypes, mechanisms, and outcomes in AD and psoriasis, with the ultimate goal of improving precision medicine and developing predictive biomarkers associated with treatment response, disease trajectories and the development of comorbidities. An existing systematic review examined biomarkers associated with AD severity;[16] however, systematic reviews regarding response to systemic therapies, disease trajectory, and comorbidities in patients with AD have not yet been performed. Thus, as one of its first steps, BIOMAP initiated systematic reviews to summarize the published evidence regarding the biomarkers for AD and psoriasis. The objective of the present systematic review was to identify which biomarkers best predict the development of comorbidities in patients with AD.

For the purpose of our systematic reviews, a biomarker is defined according to the FDA-NIH Biomarker Workgroup (2016) as a characteristic that is "measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives."[19]

2 | METHODS

2.1 | Protocol and guideline statement

This systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020193294),[20] and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidance was followed throughout.[21]

2.2 | Search strategy

One over-arching search strategy was developed by an Information Specialist (LG) to identify all published clinical evidence relevant to BIOMAP's aims, including response to systemic treatments, disease trajectory and the development of comorbidities in AD. Cochrane Database of Systematic Reviews, Cochrane Central, Embase (via Ovid), Epistemonikos, Global Resource for Eczema Trails (GREAT), Latin American and Caribbean Health Sciences Literature (LILACS), and Medline (via Ovid) were searched using relevant medical subject headings, free-text terms and study-type filters, where appropriate. Our search strategy was optimized following pilot abstract and full-text screening, as a higher than expected number of additional relevant papers were identified from citation cross-checking.

Prior to running, the final searches were quality assured and peer reviewed by a second Information Specialist using a quality assurance process based on the PRESS checklist.[22] The full strategy including population and intervention terms, study types applied, the databases searched and the years covered can be found in Appendix S1. The initial search was run on the July 31, 2020, and date limits were not applied. Searches were restricted to the English language where possible. Searches in Embase and Medline were re-run on September 20, 2021, with date limits set to identify any new evidence published since the last search.

2.3 | Study selection

Two reviewers (KVB and SL) independently screened all records identified in the search by title and abstract in Endnote. Potentially relevant articles were obtained for full-text review. The same reviewers independently assessed all full-text articles for eligibility using protocols developed using the PICO (population, intervention,

comparison, and outcome) framework. Discrepancies in the assessment were resolved through discussion, and disagreements were resolved by a third author (CB or CF). Articles were included if they were randomized studies (randomized controlled trials (RCTs)) or non-randomized studies (prospective and retrospective cohort studies, case–control studies) with relevant outcome data for investigating the association between a biomarker and predicting the development of comorbidities. For the review presented here, pre-specified comorbidities included (i) atopic comorbidities (e.g., asthma, allergic rhinoconjunctivitis (hay fever), food allergies, atopic eye disease, and eosinophilic esophagitis), (ii) other forms of dermatitis (e.g., contact dermatitis and photo-allergic contact dermatitis), (iii) a tendency to develop frequent/extensive skin infections—such as staphylococcal or herpetic infections (including eczema herpeticum) (iv) neuropsychiatric comorbidities (e.g., attention-deficit/hyperactivity disorder (ADHD), depression, and anxiety), and (v) other comorbidities in patients with AD—such as coeliac disease.

Because our aim was to identify biomarkers predictive of the subsequent development of comorbidities, longitudinal studies were selected for inclusion. Cross-sectional studies were considered relevant only when the biomarker involved was not subject to change over time (such as genetic mutations). Case-reports, case reviews, and conference abstracts were excluded. Non-English-language studies were excluded; the restriction of non-English-language studies in systematic reviews has been investigated previously with no evidence of systematic bias associated with this procedure.[23]

2.4 | Data collection process, data analysis, and risk of bias assessment

Standardized data extraction forms were created in MS Word which included study design, country, study setting, biomarkers, and comorbidities assessed, study population, recruitment details, inclusion and exclusion criteria, participants characteristics, funding and conflict of interest, outcome data, and risk of bias assessment. Data extraction forms were pre-tested prior use. Data were extracted by one author (KVB).

For dichotomous outcomes, odds ratios, risk ratios, rate ratios or hazard ratios (with 95% confidence intervals) for the independent effect of each prognostic factor (biomarker) on the outcome were extracted. In addition, sensitivity, specificity, area under the curve (AUC), negative predictive values (NPV), positive predictive values (PPV), and correlation coefficients for specific biomarkers were recorded, if reported. If a relevant summary statistic was not reported, odds ratios were preferentially calculated by the review author in Review Manager (RevMan), where possible (i.e., if sufficient data were reported to allow for calculation).[24]

Quality and risk of bias assessments were conducted by one author (KVB) for all outcomes/biomarkers using the Quality in Prognostic studies (QUIPS) checklist for prognostic studies.[25]

Extracted data and results of risk of bias assessment for each study were summarized in tables and narratively reported.

2.5 | Deviations from protocol

The protocols were amended and updated on PROSPERO prior to beginning data extraction to include studies that did not adjust for confounding (i.e., to include studies with only univariate analysis), because very few studies which adjusted for confounding were identified, and the purpose of the review was to provide an overview of available evidence and to identify areas for future research. Adjustment for confounding variables was incorporated into the quality assessment instead. A further adjustment was made to remove the requirement for two reviewers to independently perform data extraction due to staff resourcing (double-reviewing for abstract sifting and inclusion/exclusion of full-text papers was maintained). Following the updated literature search (September 2021), one author (KVB) screened all abstracts, and two authors (CB, SZ) independently evaluated selected full-texts for inclusion/exclusion. Additional data extraction was performed by SZ. Quality and risk of bias assessments were performed by KVB, to maintain consistency.

3 | RESULTS

3.1 | Included studies

The literature search identified 25,601 records from electronic databases and 29 records from manual searches; 6014 duplicate records and 4393 conference abstracts were excluded, and of the 15,194 remaining unique records, 15,020 were excluded because they did not meet the inclusion criteria (Figure 1; Appendix S2). A total of 56 papers[26–82] were included in the qualitative synthesis, reporting results from 14 prospective birth cohorts, 22 prospective cohorts, 2 retrospective cohorts, and 22 cross-sectional studies. The studies included between 37 and 1528 AD patients located in Europe ($n = 29$), America ($n = 18$), UK ($n = 6$), Asia ($n = 5$), or Australia ($n = 2$). Overall, 13 studies included both children and adults, 41 studies included only children, and 6 studies included adults only. In total, 146 different candidate biomarkers were investigated. The included studies have been summarized in Tables 1-6 and Figure 2, according to biomarker type; allergen-specific IgE (s-IgE; $n = 11$), skin prick tests (SPTs; $n = 9$), total serum IgE ($n = 7$), eosinophil count ($n = 2$), cytokine levels ($n = 2$), FLG and other skin barrier genetic variants ($n = 25$), interferon-related genetic variants ($n = 3$), other genetic variants (e.g., TSLP mutation; $n = 9$), and other biomarkers or the combination of biomarkers (e.g., airway function/s-IgE and FLG null mutations; $n = 5$). Further details regarding study populations, biomarker measurement, and analysis methods are available in Appendix S3.

3.2 | Risk of Bias

The results of the risk of bias assessment are provided in Appendix S4. For the majority of the included studies, the risk of bias was moderate to high across multiple domains. No study was classified as

having a low risk of bias across all six domains and the number of individual domains rated high risk ranged from 0 to 5. With respect to the specific domains incorporated in the QUIPS tool, the main potential source of bias arises from a lack of adjustment for confounding ($n = 47$ high,[27–38,40–47,49,50,53–61,63–65,69–71,74,75,77–79,82] $n = 11$ moderate,[26,39,48,54,66–68,73,76,80,81] and $n = 3$ low[51,52,72] risk of bias). Although, some of the included studies presented adjusted results, variables for which adjustments were made were often not clearly reported for all outcomes, or adjustments were restricted to single variables, for example, ethnicity or sex.[33–37,45,46,48,50,55,57,58,60,65,71] Study participation was another significant potential source of bias with poor reporting of key participant characteristics and recruitment details (for example, characteristics were reported for the whole study population and not reported separately for the participants with AD; $n = 34$ high risk of bias,[33–43,46–52,54–56,60,61,63,66,67,69,71,74,77,79,82] $n = 24$ moderate risk of bias,[26–30,32,44,45,53,54,56–59,63–65,68,72,75,76,78,80,81] and $n = 3$ low risk of bias[31,70,73]). The included studies frequently suffered from loss-to-follow-up (QUIPS study attrition domain). Fourteen and 17 studies showed a high[26,28,29,33,43,54–59,61,69,79] or moderate[33,34,37,40,46,47,50–52,54,64,68,70–72,80,81] risk of bias in the domain of prognostic factor measurement, primarily because of incomplete details of biomarker measurement. While outcome assessment was frequently by means of parental report and/or questionnaire, the included studies provided adequate details and this domain was predominantly at low[29,31–37,39,42,46–48,50,52,54,56,60,63,67,68,70,72–75,77–79] or moderate[26–28,30,33,38,40,41,44,45,51,53–59,61,63–66,69,71,76,80–82] risk of bias. Statistical analysis and reporting was adequate, and 44 of the studies[26–28,30–33,36,38–41,44,45,47,48,52–56,58,61,63–66,70,71,73–75,77–81] were classified as being of low risk of bias ($n = 2$ high risk of bias[49,50] and $n = 17$ moderate risk of bias[29,34,35,37,42,43,46,51,57,59,60,67–69,72,76,82]).

3.3 | Comorbidities

3.3.1 | Asthma

Forty-two articles reported results from 36 different cohorts investigating the association between candidate biomarkers and the development of asthma and/or wheeze (Table 1). Ten studies examined specific IgE (s-IgE) to 10 food and/or inhalant allergens, and reported results for individual s-IgE or as a composite assessment of multiple food and/or inhalant allergens.[26,29,33,40,55,66–68,78,82] Across all 10 studies, children sensitized to one or more allergens were more likely to develop asthma, than those without allergic sensitization, but the strength of this association varied and the reported odds ratios (ORs) or relative risk (RR) ranged from 1.1 to 6.3. Furthermore, the age at which biomarkers was measured (1–184 months), and at which asthma or wheezing was diagnosed (1–22 years) varied widely. Statistically significant associations were demonstrated for sensitivity to any allergen,[26] any food allergen,[29,33,40,55] any inhalant allergen,[29,67] egg alone,[66,78] egg and/or milk,[68] cat dander,[78] grass,[78] and house dust mite,[78,82] but not for elevated s-IgE for cat and/or mite.[68] Eight studies reported outcomes for allergic sensitization based on positive skin prick tests (SPTs).[29,51,52,61,64,67,72,76] Compared

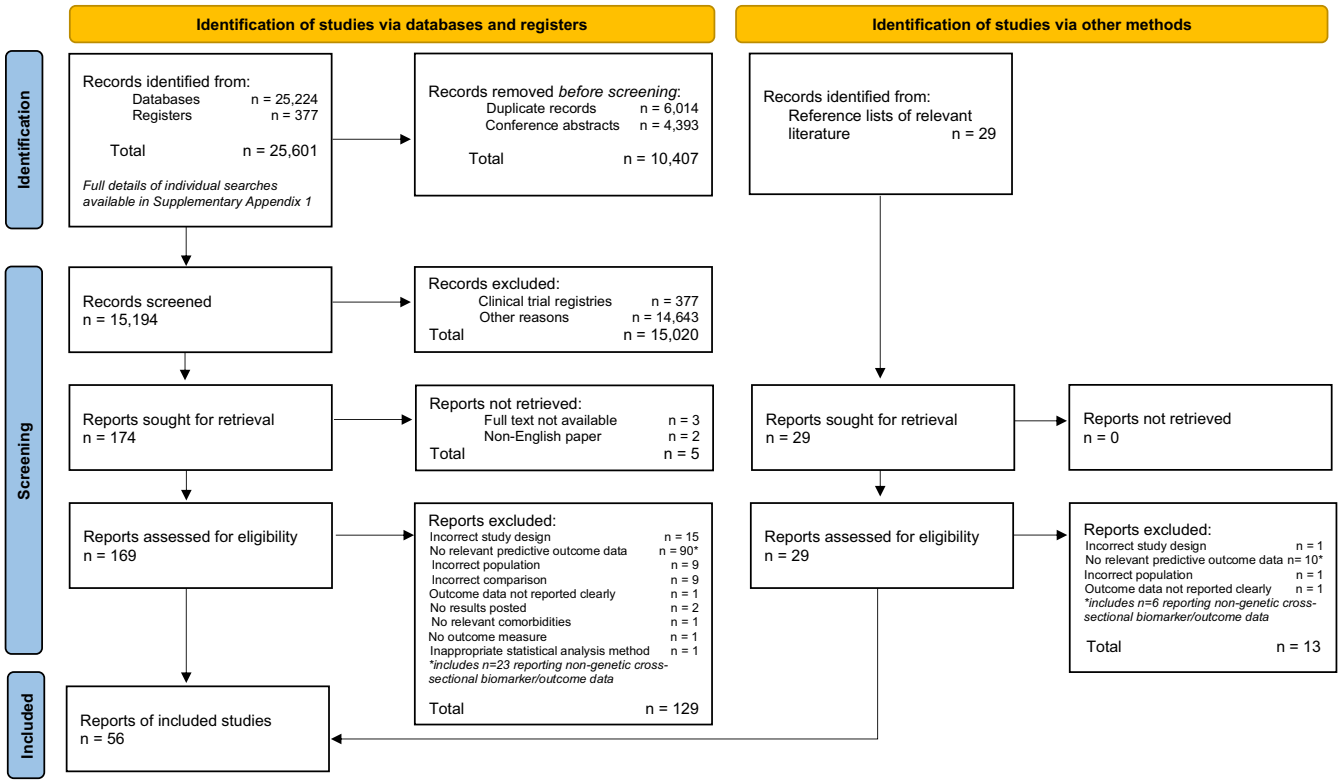

FIGURE 1 PRISMA 2020 flow diagram for the systematic review of biomarkers predicting development of comorbidities in atopic dermatitis

TABLE 1 Overview: Studies evaluating biomarkers predictive of asthma and wheezing

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result: measures of effect (95% CI)	Result summary	Analysis
Allergen specific IgE (α, α-lactalbumin; a, apple; al, alternaria; ahf, animal hair-fur; β, β-lactoglobulin; b, birch; c, cat; ca, casein; ch, cladosporium herbarium; co, cod; d, dog; dp, dermatophagoides pteronyssinus; e, egg; f, fish; fl, flour; g, grass; h, horse; hd, house dust; hdm, house dust mites; m, milk; mu, mugwort; n, nut; p, peanut; s, soy; t, timothy; w, weed; wh, wheat)						
Ballardini 2014[26] *n* = 137 (children)	Prospective birth cohort, multicenter (population-based)	Any (b, c, ch, co, d, dp, e, h, m, mu, p, s, t, wh) Measured at 2 years of age	Asthma (questionnaire report of symptoms or treatment) Assessed at 12 years of age	Significant: OR 3.19 (1.20–8.50)	▲	Adjusted
Cosickic 2017[29] *n* = 114 (children)	Prospective cohort, single center (pediatric department)	Food (e, m, f, fl, p, s) Inhalant (ahf, dp, hd, g, w) Measured at median age 26.5 (range 1.5–96) months and yearly over 5 years	Asthma (physician-diagnosed) Assessed between 5.1–13 years of age	Significant: OR 5.4 (1.6–17.2) Significant: OR 6.1 (1.3–28.6)	▲ ▲	Adjusted
Filipiak Pittroff 2011[33] *n* = 186 (children)	RCT/prospective birth cohort, multicenter (risk-enriched sample; family history of allergic disease)	Food (α, β m, ca, e, s) Measured at 12 and at 36 months of age	Asthma (parental report of physician-diagnosis) Assessed between 7–10 years of age	NS: OR 1.7 (0.5–5.7)	△	Adjusted
Filipiak Pittroff 2011[33] *n* = 192 (children)			Wheezing (questionnaire report of symptoms) Assessed at 10 years of age	NS: OR 2.13 (0.93–4.89)	△	Crude
Filipiak Pittroff 2011[33] *n* = 240 (children)	Prospective birth cohort, multicenter (population-based)	Food (co, e, m, p, s, wh) Measured at 2 years of age	Asthma (parental report of physician-diagnosis) Assessed between 7–10 years of age	Significant: OR 6.3 (1.8–22.5)	▲	Adjusted
Filipiak Pittroff 2011[33] *n* = 233 (children)			Wheezing (questionnaire report of symptoms) Assessed at 10 years of age	Significant: OR 4.40 (1.81–10.67)	▲	Crude
Gustafsson 2000[40] *n* = 94 (children)	Prospective cohort, multicenter (allergy clinic or child welfare clinic)	Food (co, e, m, p, s, wh) Measured before 36 months of age	Asthma (physician-diagnosed) Assessed between 5–8 years of age	Significant: OR 4.95 (1.97–12.43)	▲	Crude
Marenholz 2009[55] *n* = 180 (children)	Prospective birth cohort, multicenter (risk-enriched sample; 38% high allergy risk)	Food (e, m, s, wh) Measured in first 3 years of life, at least 2 timepoints	Asthma (report of symptoms) Assessed at 13 years of age	Significant: RR 2.36 (1.58–3.52)	▲	Crude
Ohshima 2002[82] *n* = 92–139 (children)	Prospective cohort, multicenter (pediatric outpatient clinics)	House dust mite Measured before 12 months of age and yearly over 4 years	Asthma (physician-diagnosed) Assessed between 1–4 years of age	NS: 1-year follow-up OR 3.53 (0.82–15.15) Significant: 2-year follow-up OR 3.97 (1.18–13.33) Significant: 3-year follow-up OR 4.37 (1.22–15.63) Significant: 4-year follow-up OR 4.16 (1.17–14.70)	△ ▲ ▲ ▲	Crude

TABLE 1 (Continued)

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result: measures of effect (95% CI)	Result summary	Analysis
Ricci 2006[66] *n* = 205 (children and adolescents)	Retrospective cohort with a prospective follow-up interview, single center (tertiary center)	Egg	Asthma (questionnaire and medical records) Age inclusion for assessment between 6–36 months, mean 16.9 year f/u	Significant: OR 2.23 (1.10–4.49)	▲	Adjusted
		Cow's milk		NS: OR 1.24 (0.58–2.65)	△	Crude
		Inhalant (al, c, d, g, h, hdm) Measured between 6–36 months of age		NS: OR 1.92 (0.99–3.72)	△	
Ricci 2010[67] *n* = 176 (children)	Retrospective cohort with a prospective follow-up interview, single center (tertiary center)	Egg	Asthma (diagnosed by GP or pediatric allergist/ pulmonologist) Mean age inclusion for assessment 11.7 (±NR) months, mean 7.5 year f/u	NS: OR 2.09 (0.94–4.66)	△	Crude
		Cow's milk		NS: OR 2.04 (0.92–4.52)	△	
		Food (a, co, e, m, n, p, s, wh)		NS: OR 1.82 (0.78–4.25)	△	
		Inhalant (c, d, g, hdm) Measured at mean age 11.7 (±NR) months		Significant: OR 4.22 (1.19–14.95)	▲	Adjusted
Sarria 2014[68] *n* = 94 (children with biomarker data at baseline)	Prospective cohort, single center (risk-enriched; increased atopy and family history of asthma; pediatric clinic)	Egg and/or cow's milk Measured at baseline	Asthma (physician-diagnosis and report of symptoms past 12 months; use of asthma treatments) Assessed at 4 years of age	Significant: OR 2.66 (1.10–6.45)	▲	Adjusted
		Cat and/or house dust mite Measured at baseline		NS: OR 1.86 (0.86–4.00)	△	
		Inhalant Measured at baseline, median age 10.7 months (range 2.6–19.1)		NS: OR 3.62 (0.72–18.29)	△	
n = 94 (children with biomarker data after 1-year follow-up)		Egg and/or cow's milk Measured at 1-year f/u		Significant: OR 2.89 (1.11–7.51)	▲	
		Cat and/or house dust mite Measured at 1-year f/u		NS: OR 1.19 (0.71–1.99)	△	
		Inhalant Measured at 1-year f/u		NS: OR 1.46 (0.69–3.10)	△	
Warner 2001[78] *n* = unclear (children)	RCT/prospective cohort, (risk-enriched sample; family history of atopic disease; unclear setting)	Egg	Asthma (clinical diagnosis based on report of symptoms) Mean age inclusion for assessment 17.2 (±4.1) months, 36 months f/u	Significant: RR 1.4 (1.1–1.7)	▲	Crude
		Milk		NS: RR 1.1 (0.9–1.4)	△	
		Grass		Significant: RR 1.7 (1.4–2.1)	▲	
		House dust mite		Significant: RR 1.6 (1.3–1.9)	▲	
		Cat dander Measured at mean age 17.2 (±4.1) months		Significant: RR 1.5 (1.2–1.9)	▲	
SPT (ahf, animal hair-fur; al, alternaria; ar, artemisia; b, bacteria; c, cat; co, cod; coc, cockroach; cs, cupressus semprecires; e, egg; fa, fabrics; fe, feathers; fl, flour; fr, fuit; fu, fungi; h, hazel; hd, house dust; hdm, house dust mite; m, milk; me, meat; mu, mugwort; o, olive tree; p, peanut; pa, parietaria; po, poplar; to, tomato; tr, tree; v, vegetables; w, weed; wh, wheat)						
Cosickic 2017[29] *n* = 114 (children)	Prospective cohort, single center (pediatric department)	Food (e, m, fl, me l and II, fr I, II and III, v I and II)	Asthma (physician-diagnosed) Assessed between 5.1–13 years of age	Significant: OR 5.0 (2.1–11.8)	▲	Crude
		Inhalant (ahf, b, fa, fe, fu, g, hd, hdm, tr, w, v) Measured at median age 26.5 (range 1.5–96) months and yearly over 5 years		Significant: OR 10.7 (3.7–30.9)	▲	

(Continues)

TABLE 1 (Continued)

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result: measures of effect (95% CI)	Result summary	Analysis
Lodge 2011[51] *n* = NR (children)	Prospective birth cohort, single center (risk-enriched sample; family history of atopy)	House dust mite Measured at 1 year of age	Wheeze (questionnaire report of symptoms) Assessed at 12 years of age	NS: OR 2.7 (0.96–7.62)	△	Adjusted
Lowe 2007[52] *n* = 189 (children)	Prospective birth cohort, single center (risk-enriched sample; family history of atopy)	Any (c, e, g, hdm, m, p) Measured at6 months, 1 year, 2 years of age	Asthma (physician-diagnosed based on symptoms) Assessed between 6–7 years of age	Significant: OR 2.60 (1.32–5.14)	▲	Adjusted
Novembre 2011[61] *n* = 77 (children)	Cohort study (unclear if prospective or retrospective), single center (allergy unit)	Any (al, e, c, co,cs, d, g, hdm, m, mu, o, pa, s, to, wh) Measured at 2 years of age	Asthma (NR) Assessed at 11 years of age	Significant: OR 8.7 (2.61–28.9)	▲	Crude
Piancatelli 2008[64] *n* = 27 (children)	Prospective cohort, single center (setting unclear)	Any (al, ar, c, e, h, hdm, m, o, po, w) Measured at 1–184 months of age	Asthma or rhinoconjunctivitis (NR) Age range inclusion for assessment 1–184 months, 3 years f/u	NS: OR 11.9 (0.59–237.4)	△	Crude
Ricci 2010[67] *n* = 176 (children)	Retrospective cohort with a prospective follow-up interview, single center (tertiary center)	Egg	Asthma (diagnosed by GP or pediatric allergist/pulmonologist) Mean age inclusion for assessment 11.7 months, mean 7.5 years f/u	Significant: OR 2.53 (1.12–5.71)	▲	Crude
		Cow's milk		Significant: OR 2.88 (1.28–6.50)	▲	
		Food (a, co, e, m, n, p, s, wh)		Significant: OR 4.00 (1.54–10.36)	▲	
		Inhalant (al, c, d, g, hdm) Measured at mean age 11.7 (±NR) months		NS: OR 1.51 (0.39–5.86)	△	Adjusted
Tran 2018[72] *n* = 265 (children)	Prospective birth cohort, multicenter (population-based)	Food (e, m, p, s)	Asthma (physician diagnosis based on clinical history) Assessed at 3 years of age	Significant: RR 6.21 (2.25–17.2)	▲	Adjusted
		Inhalant (al, c, coc, d, dp, df, hdm)		Significant: RR 2.95 (1.06–8.24)	▲	
		Any (al, c, coc, d, e, hdm, m, p, s) Measured at 1 year of age		Significant: RR 12.46 (3.06–50.8)	▲	
Wang 2015[76] *n* = 397 (children)	Prospective cohort, multicenter (population-based)	House dust mite	Asthma (asthma symptoms or medication use ± clinical signs on examination) Assessed at 6 years of age	Significant: OR 1.89 (1.10–3.25)	▲	Adjusted
		Cockroach		NS: OR 2.22 (0.67–7.36)	△	
		Dog		NS: OR 1.55 (0.14–17.3)	△	Crude
		Milk		NS: OR 3.16 (0.63–15.9)	△	
		Egg		NS: OR 1.03 (0.11–10.0)	△	
		Crab Measured at 3 years of age		NS: OR 0.61 (0.03–12.9)	▽	

TABLE 1 (Continued)

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result: measures of effect (95% CI)	Result summary	Analysis
Total serum IgE						
Cosickic 2017[29] *n* = 114 (children)	Prospective cohort, single center (pediatric department)	Total serum IgE > 100 IU/ml Measured at median age 26.5 (range 1.5–96) months and yearly over 5 years	Asthma (physician-diagnosed) Assessed between 5.1–13 years of age	Significant: OR 8.4 (2.9–24.0)	▲	Adjusted
Piancatelli 2008[64] *n* = 27 (children)	Prospective cohort, single center (setting unclear)	Total serum IgE (Age-specific reference ranges [U/ml]: 2–5 years, >60; 6–9 years, >75; 10–13 years, >155; >13 years, >I00) Measured at 1–184 months of age	Asthma or rhinoconjunctivitis (NR) Age range inclusion for assessment 1–184 months, 3 years f/u	NS: OR 8.0 (0.82–77.8)	△	Crude
Ricci 2006[66] *n* = 205 (children and adolescents)	Retrospective cohort with a prospective follow-up interview, single center (tertiary center)	Total serum IgE age-specific NR Measured at 6–36 months of age	Asthma (questionnaire and medical records) Age inclusion for assessment between 6–36 months, mean 16.9 years f/u	NS: OR 1.04 (0.58–1.85)	△	Crude
Ricci 2010[67] *n* = 176 (children)	Retrospective cohort with a prospective follow-up interview, single center (tertiary center)	Total serum IgE > 0.35 kU/L Measured at mean age 11.7 (±NR) months	Asthma (diagnosed by GP or pediatric allergist/pulmonologist) Mean age inclusion for assessment 11.7 months, mean 7.5 years f/u	Significant: OR 2.45 (1.04–5.74)	▲	Crude
Sarria 2014[68] *n* = 114 (children at baseline) *n* = 112 (children at 1 year)	Prospective cohort, single center (risk-enriched; increased atopy and family history of asthma; pediatric clinic)	Total serum IgE NR Measured at baseline, median age 10.7 months (range 2.6–19.1) Measured at 1 year f/u	Asthma (physician-diagnosis and report of symptoms past 12 months; or use of asthma treatments) Assessed at 4 years of age	Significant: OR 1.33 (1.02–1.74) NS: OR 1.29 (0.99–1.69)	▲ ▲	Adjusted
Wahn 1998[75] *n* = 357 (children)	RCT/prospective cohort, (risk-enriched sample; family history of atopic disease; unclear setting)	Total serum IgE >30 kU/L Measured at mean age 17.2 (±4.1) months	Asthma (clinical diagnosis based on report of symptoms) Assessed between 28–43 months of age	Significant: RR 1.3 (1.0–1.7), *p*-value = 0.027	▲	Crude
Wang 2015[76] *n* = 397 (children)	Prospective cohort, multi-center (population-based)	Total serum IgE not appropriate (continuous) Measured at 3 years of age	Asthma (asthma symptoms or medication use ± clinical signs on examination) Assessed at 6 years of age	NS: Median baseline IgE in participants who developed asthma: 154.0 (range 749) Median baseline IgE in participants who did not develop asthma: 97.1 (range 554) *p*-value = 0.09	△	Crude

(Continues)

TABLE 1 (Continued)

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result: measures of effect (95% CI)	Result summary	Analysis
Cytokine profiles						
Sarria 2014[68] *n* = 94 (children at baseline) *n* = 94 (children at 1 year)	Prospective cohort, single center (risk-enriched; increased atopy and family history of asthma; pediatric clinic)	IL-4/IFN-γ, IL-5/IFN-γ, IL-9/IFN-γ, IL-10/IFN-γ, IL-13/IFN-γ, and IL-17/IFN-γ ratios Measured at baseline, median age 10.7 months (range 2.6–19.1)	Asthma (physician-diagnosis and report of symptoms past 12 months; use of asthma treatments) Assessed at 4 years of age	Significant: IL-4/IFN-γ OR 3.42 (1.15–10.17)	▲	Adjusted
				Significant: IL-10/IFN-γ OR 6.46 (1.28–32.51)	▲	
				NS: IL-5/IFN-γ OR 1.85 (0.902–3.79)	△	
				NS: IL-9/IFN-γ OR 1.51 (0.793–2.87)	△	
				NS: IL-13/IFN-γ OR 1.23 (0.76–1.99)	△	
				NS: IL-17/IFN-γ OR 1.29 (0.79–2.09)	△	
		IL-4/IFN-γ, IL-5/IFN-γ, IL-9/IFN-γ, IL-10/IFN-γ, IL-13/IFN-γ, and – 17/IFN-γ ratios Measured again after 1-year f/u		NS: IL-4/IFN-γ OR 0.68 (0.42–1.11)	▽	Adjusted
				NS: IL-5/IFN-γ OR 0.89 (0.54–1.48)	▽	
				NS: IL-9/IFN-γ OR 2.46 (0.96–6.30)	△	
				NS: IL-10/IFN-γ OR 0.75 (0.45–1.26)	▽	
				NS: IL-13/IFN-γ OR 0.84 (0.51–1.40)	▽	
				NS: IL-17/IFN-γ OR 0.76 (0.44–1.31)	▽	
Yao 2010[80] *n* = 114 (children)	Prospective cohort, single center (risk-enriched; increased atopy and family history of asthma; pediatric clinic)	IL-4/IFN-γ, IL-5/IFN-γ, IL-10/IFN-γ and IL-13/IFN-γ ratio Measured at median age 10.7 months (range 2.6–19.1)	Wheezing episodes (phone report of symptoms) Median age inclusion for assessment 10.7 months (range 2.6–19.1), 1 year f/u	Significant: IL-4/IFN-γ RR 1.33 (1.11–1.6)	▲	Adjusted
				Significant: IL-5/IFN-γ RR 1.33 (1.1–1.62)	▲	
				Significant IL-10/IFN-γ RR 1.35 (1.14–1.59)	▲	
				NS: IL-13/IFN-γ RR 1.11 (0.93–1.34)	△	
Eosinophils						
Cosickic 2017[29] *n* = 114 (children)	Prospective cohort, single center (pediatric department)	Eosinophils count ≥0.45×10^9/L Measured at median age 26.5 (range 1.5–96) months and yearly over 5 years	Asthma (physician-diagnosed) Assessed between 5.1–13 years of age	Significant: OR 9.1 (2.9–28.0)	▲	Adjusted

TABLE 1 (Continued)

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result: measures of effect (95% CI)	Result summary	Analysis
Wahn 1998[75] *n* = 357 (children)	RCT/prospective cohort, (risk-enriched sample; family history of atopic disease; unclear setting)	Eosinophils count >0.7 x 10^9/L Measured at mean age 17.2 (±4.1) months	Asthma (clinical diagnosis based on report of symptoms) Assessed between 28–43 months of age	NS: RR 1.4 (1.0–1.9), *p*-value = 0.066	△	Crude
FLG and other skin barrier genetic variants						
Bonnelykke 2010[27] *n* = NR (children)	Prospective birth cohort, single center (risk-enriched sample; mothers with asthma)	R501X or 2282del4	Asthma (clinically assessment and symptom diary) Assessed between 0–5 years of age	NS: OR 1.82 (0.63–5.21)	△	Crude
			Acute severe asthma exacerbation incidence (clinically assessment and symptom diary) Assessed between 0–5 years of age	NS: IR: 2.52 (0.97–6.55)	△	
			Asthma-related events (recurrent wheeze or acute severe asthma exacerbation) (clinically assessment and symptom diary) Assessed between 0–5 years of age	NS: HR: 1.65 (0.82–3.32)	△	
Chang 2017[28] *n* = 842 (children)	Prospective cohort, multicenter (secondary and primary care)	R501X, 2282del4, R2447X, or S3247X	Asthma (NR) Assessed at 7.2 years of age	Significant: OR 1.52 (1.05–2.20)	▲	Crude
Debinska 2017[30] *n* = 87 (children)	Prospective cohort, single center (general population)	R501X, 2282del4, R2447X, or S3247X	Asthma (report of symptoms or physician diagnosis) Assessed between 3–4 years of age	NS: OR 1.20 (0.27–5.08)	△	Crude
Filipiak Pittroff 2011[33] *n* = 137 (children)	RCT/prospective birth cohort, multicenter (risk-enriched sample; family history of allergic disease)	R501X or 2282del4	Asthma (parental report of physician-diagnosis) Assessed between 7–10 years of age	Significant: OR 3.8 (1.0–14.2) *p*-value = 0.02	▲	Adjusted
Filipiak Pittroff[33] *n* = 140 (children)			Wheezing (questionnaire report of symptoms) Assessed at 10 years of age	NS: OR 1.43 (0.43–4.79)	△	Crude
Filipiak Pittroff 2011[33] *n* = 149 (children)	Prospective birth cohort, multicenter (population-based)		Asthma (parental report of physician-diagnosis) Assessed between 7–10 years of age	NS: OR 1.8 (0.4–7.1)	△	Adjusted
Filipiak Pittroff 2011[33] *n* = 148 (children)			Wheezing (questionnaire report of symptoms) Assessed at 10 years of age	Significant: OR 4.03 (1.10–14.80)	▲	Crude
Filipiak Pittroff 2011[33] *n* = 65 (children)	Prospective cohort, multicenter (risk-enriched sample; 50% with known food allergy)	R501X, 2282del4, R2447X, or S3247X	Asthma (parent report of doctor-diagnosis) Mean age at assessment NR, 8 years f/u	NS: OR 0.64 (0.21–1.98)	▽	Crude
Greisenegger 2010[38] *n* = 438 (adults)	Cross-sectional study, multicenter (allergy or dermatology outpatient clinics)	R501X, 2282del4, R2447X, or S3247X	Asthma (NR) Assessed at median age of 31 years	NS: OR 1.27 (0.79–2.05)	△	Crude

(Continues)

TABLE 1 (Continued)

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result: measures of effect (95% CI)	Result summary	Analysis
Heede 2017[42] *n* = 227 (adults)	Cross-sectional study, single center (dermatology department)	R501X, 2282del4, or R2447X	Asthma (self-reported lifetime prevalence of doctor's diagnosis) Assessed at median age of 42 years	NS: OR 1.40 (0.78–2.54)	△	Crude
Henderson 2008[43] *n* = NR (children)	Prospective birth cohort, multicenter (population-based)	R501X or 2282del4	Early wheeze (questionnaire report of symptoms) Assessed at up to 42 months of age	NS: OR 1.26 (0.94–1.69)	△	Crude
Holm 2019[45] *n* = 141 (adults/children)	Cross-sectional study, single center (dermatology outpatient department)	R501X, 2282del4, or R2447X	Asthma (early-onset) (questionnaire report of symptoms) Assessed at mean age 18.7 (±16.5) years	Significant: OR 2.27 (1.09–4.75)	▲	Crude
n = 153 (adults/children)			Asthma (late-onset) (questionnaire report of symptoms) Assessed at mean age 18.7 (±16.5) years	NS: OR 2.15 (0.97–4.75)	△	
Lesiak 2011[49] *n* = 163 (adults and children)	Cross-sectional study, setting unclear	2282del4	History of early-onset asthma (NR) Assessed before age of 3 years	Significant: OR 11.34 (1.47–87.3)	▲	Crude
		R501X or 2282del4		Significant: OR 10.5 (1.46–76.3)	▲	
Luukkonen 2017[53] *n* = 434 (adults and children)	Prospective cohort, single center (skin and allergy hospital)	R501X	Asthma (NR) Mean age inclusion for assessment 32.3 (±14.9) years, 1 year f/u	Significant: OR 8.78 (1.07–72.1)	▲	Crude
		2282del4		NS: OR 1.64 (0.78–3.47)	△	
		R2447X		NS: OR 1.05 (0.31–3.48)	△	
		R501X, 2282del4, or R2447X		NS: OR 1.76 (0.96–3.22)	△	
Marenholz 2006[56] *n* = 890 (children)	Cross-sectional study, multicenter (family-based association)	R501X or 2282del4	Asthma (parent report of doctor-diagnosis) Mean age inclusion for assessment 7.9 (±NR) years	Significant: OR 1.38 (1.08–1.78)	▲	Crude
Marenholz 2006[56] *n* = 186 (children)	Prospective birth cohort, multicenter (risk-enriched sample; 38% high allergy risk)	R501X or 2282del4	Asthma (one or more wheezing episodes during the previous 12 months) Assessed at 7 and/or 10 years of age	Significant: OR 11.8 (1.2–116.3)	▲	Crude
Marenholz 2009[55] *n* = 229 (children)	Prospective birth cohort, multicenter (risk-enriched sample); 38%	R501X or 2282del4	Asthma (report of symptoms) Assessed at 13 years of age	Significant: overall OR 2.17 (1.06–4.46)	▲	Crude
Marenholz 2009[55] *n* = 180 (children who also had s-IgE data)				NS: non-food sensitized subgroup 0.58 (0.16 to 2.13)	▽	
				Significant: food sensitized subgroup OR 26.7 (1.47–485.6)	▲	

TABLE 1 (Continued)

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result: measures of effect (95% CI)	Result summary	Analysis
Margolis 2019[59] *n* = NR (741 included in study, 399 with asthma; 342 without, children)	Prospective cohort, multicenter (secondary and primary care)	24 FLG variants	Asthma (NR) Age at assessment NR	NS: OR 1.34 (0.95–1.89)	△	Crude
Palmer 2006[63] *n* = 142 (children)	Prospective birth cohort, single center (risk-enriched sample; mothers with asthma)	R501X or 2282del4	Asthma (clinically assessment and symptom diary) Assessed between 0–3 years of age	NS: OR 1.14 (0.39–3.39)	△	Crude
Palmer 2006[63] *n* = 52 (children)	Cross-sectional study, single center (setting unclear)	R501X or 2282del4	Asthma (physician-diagnosed based on symptoms) Assessed between 1–16 years of age	NS: OR 1.10 (0.36–3.35)	△	Crude
Schuttelaar 2009[69] *n* = NR (children)	Prospective birth cohort, multicenter (risk-enriched, 67% of mothers were allergic; midwifery practices)	R501X, 2282del4, or R2447X	Asthma (parental report of physician-diagnosis and presence of symptoms in previous 12 months) Assessed between 0–8 years of age	Significant: OR 3.2 (1.2–8.5)	▲	Crude
Wang 2011[77] *n* = 116 (children)	Cross-sectional study, multicenter (hospital-based clinics)	P478S polymorphism (rs11584340)	Asthma (parental report of doctor's diagnosis) Age at assessment NR	Significant: OR 4.68 (1.37–16.03)	▲	Crude
Wang 2015[76] *n* = 397 (children)	Prospective cohort, multicenter (population-based)	P478S polymorphism (rs11584340)	Asthma (asthma symptoms or medication use ± clinical signs on examination) Assessed at 6 years of age	Significant: OR 2.26 (1.33–36.84)	▲	Adjusted
Weidinger 2008[79] *n* = 540 (children)	Cross-sectional study within prospective cohort study, multicenter (community-based)	R501X, 2282del4, or 3702delG	Asthma or atopic asthma (parent-report of doctor's diagnosis; atopic asthma additionally requires positive SPT, NR in AD group) Mean age of assessment in overall study population 9.6 (±0.6) years	NS: asthma OR 1.52 (0.83–2.77) NS: atopic asthma OR 1.65 (0.77–3.54)	△ △	Crude
Ziyab 2014[81] *n* = NR (Overall: *k* = 577, *k* = 159 with asthma; Sensitized: *k* = 210, *k* = 92 with asthma; Non-sensitized: *k* = 291, *k* = 45 with asthma, children)	Prospective birth cohort, multi-center (population-based)	R501X, 2282del4, or S3247X	Asthma (questionnaire based) Assessed between 1–18 years of age	Significant: overall RR 1.56 (1.10–2.21) Significant: food and inhalant-sensitized subgroup RR 2.11 (1.49–2.99) NS: non-food and inhalant-sensitized subgroup RR 0.54 (0.18 to1.63)	▲ ▲ ▽	Adjusted

(Continues)

TABLE 1 (Continued)

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result: measures of effect (95% CI)	Result summary	Analysis
Hertz 2020[44] *n* = 43 (adults/children)	Cross-sectional study, multicenter (dermatology outpatient departments)	FLG-2 rs12568784 FLG-2 rs16833974	Asthma (NR) Age categories for assessment 0->20 years of age	NS: OR 0.63 (0.19–2.13) NS: OR 2.11 (0.34–13.0)	▽ △	Crude
Margolis 2014[57] *n* = 299 (children, African American)	Prospective cohort, multicenter (secondary and primary care)	FLG-2 variants (rs12568784, rs150529054, Q2053del224)	Asthma (NR) Assessed at mean age 6.8 (±NR) years	NS: rs12568784 OR 1.05 (0.70–1.57) NS: rs150529054 OR 1.12 (0.66–1.90) NS: Q2053del224 OR 0.88 (0.34–2.32)	△ △ ▽	Crude
TSLP genetic variants						
Chang 2017[28] *n* = 770 (children)	Prospective cohort, multicenter (secondary and primary care)	TSLP SNP - rs1898671	Asthma (NR) Assessed at mean age 7.2 (±3.8) years	NS: OR 1.34 (0.95–1.89)	△	Crude
Margolis 2014[58] *n* = 732 (children, 45.6% African American)	Prospective cohort, multicenter (secondary and primary care)	TSLP SNP - rs1898671	Asthma (NR) Mean age inclusion for assessment 7.1 (±3.1) years, mean 5.7 years f/u	NS: overall: OR 1.02 (0.81–1.30) NS: White: OR 1.11 (0.81–1.50) NS: African American: OR 1.07 (0.64–1.80)	△ △ △	Crude
Other genetic variants						
Greisenegger 2013[39] *n* = 249 (adults)	Cross-sectional study, multicenter (allergy or dermatology outpatient clinics)	HRNR gene – rs877776 rs7927894 (chromosome 11q13 SNP)	Asthma (NR) Assessed at median age of 28 years	NS: OR and CI not reported NS: OR 0.95 (0.51–1.75)	NR ▽	Adjusted
Kayserova 2012[47] *n* = 74 (children)	Prospective cohort, multicenter (dermatology and immunology departments)	IL10R gene polymorphism	Asthma (clinical manifestations) Assessed between 0–3 years of age	NS: 1082A/G: *p*-value = 0.880 NS: 819C/T: *p*-value = 0.467 NS: 529A/C: *p*-value = 0.471	≈ ≈ ≈	Crude
		IL4Rα gene polymorphism		NS: 1902A/G: *p*-value = 0.334	≈	Crude
Marenholz 2011[54] *n* = 715 (children)	Prospective birth cohort, multicenter (population-based)	rs7927894 (T risk allele) (chromosome 11q13 SNP)	Asthma (questionnaire and parent report of doctor-diagnosis) Assessed at 13 years of age	Significant: OR 1.45 (1.12–1.86)	▲	Adjusted
Marenholz 2011[54] *n* = 682 (children)	Cross-sectional study, multicenter (family-based association)	rs7927894 (T risk allele) (chromosome 11q13 SNP)	Asthma (parent report of doctor-diagnosis) Assessed at mean age 7.9 (±NR) years	Significant: OR 1.38 (1.08–1.78)	▲	Crude

TABLE 1 (Continued)

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result: measures of effect (95% CI)	Result summary	Analysis
Potaczek 2011[65] *n* = 27 (adults, unclear if also children)	Cross-sectional study, setting unclear	TLR2-16934 A>T polymorphism (A allele)	Asthma (diagnosed based on typical symptoms and spirometry criteria based on GINA 2008 guidance) Assessed at mean age 29.6 (±0.98) years	Significant: overall OR 5.19 (1.15–23.4)	▲	Crude
				Significant: stratified by IgE ≥106: OR 8.50 (2.30–31.47)	▲	
				NS: stratified by IgE < 106: OR 1.00 (0.24–4.22)	≈	
		TLR2-16934 A>T polymorphism (AA genotype)		Significant: overall OR 3.02 (1.30–6.98)	▲	
				NS: stratified by IgE ≥106: OR 8.21 (0.98–69.0)	△	
				NS: stratified by IgE <106: OR 3.00 (0.35–25.6)	△	
Tsunemi 2004[74] *n* = 134 (adults)	Cross-sectional study, setting unclear	CCR4 gene - C1014T SNP (T allele)	Asthma (clinical diagnosis according - NAEPP EPR-2 guidelines) Assessed at mean age 27.4 (±7.7) years	Significant: OR 0.05 (0.003–0.94)	▼	Crude
Other biomarkers						
Filipiak Pittroff 2011[33] *n* = 111 (children)	RCT/prospective birth cohort, multicenter (risk-enriched sample; family history of allergic disease)	FLG (R501X or 2282del4) *and any* food s-IgE (combined biomarkers) Measured s-IgE at 12 and 36 months of age	Asthma (parental report of physician-diagnosis) Assessed between 7–10 years of age	NS: OR 2.80 (0.49–15.95)	△	Crude
Filipiak Pittroff 2011[33] *n* = 114 (children)			Wheezing (questionnaire report of symptoms) Assessed at 10 years of age	NS: OR 2.28 (0.41–12.75)	△	
Filipiak Pittroff 2011[33] *n* = 139 (children)	Prospective birth cohort, multicenter (population-based)	FLG (R501X or 2282del4) *and* any food s-IgE (combined biomarkers) Measured s-IgE at 2 years of age	Asthma (parental report of physician-diagnosis) Assessed between 7–10 years of age	NS: OR 5.29 (0.82–34.25)	△	Crude
Filipiak Pittroff 2011[33] *n* = 138 (children)			Wheezing (questionnaire report of symptoms) Assessed at 10 years of age	Significant: OR 6.72 (1.02–44.27)	▲	
Marenholz 2009[55] *n* = 180 (children)	Prospective birth cohort, multicenter (risk-enriched sample; 38% high allergy risk)	FLG (R501X, 2282del4 or R2447X) *and* any food s-IgE (combined biomarkers) Measured in first 3 years of life, at least 2 timepoints	Asthma (report of symptoms) Assessed at 13 years of age	Significant: FLG+/sensitized vs. FLG−/non-sensitized RR 4.07 (2.94–5.65)	▲	Crude
				NS: FLG+/non-sensitized vs. FLG−/non-sensitized RR 0.64 (0.22–1.91)	▽	
				Significant: FLG−/sensitized vs. FLG−/non-sensitized RR 1.79 (1.11–2.88)	▲	

(Continues)

TABLE 1 (Continued)

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result: measures of effect (95% CI)	Result summary	Analysis
Wang 2015[76] *n* = 397 (children)	Prospective cohort, multicenter (population-based)	FLG P478S polymorphism (rs11584340) (TT) *and* house dust mite SPT sensitization Evaluated at 3 years of age	Asthma (asthma symptoms or medication use ± clinical signs on examination) Assessed at 6 years of age	Significant: for TT / sensitized OR: 4.78 (2.51–9.11)	▲	Crude
				NS: for TC + CC / sensitized OR: 1.01 (0.51–2.00)	△	
				NS: for TT/ non-sensitized OR: 1.34 (0.70–2.56)	△	
Sarria 2014[68] *n* = 114 (children at baseline) *n* = 112 (children at 1 year)	Prospective cohort, single center (risk-enriched; increased atopy and family history of asthma; pediatric clinic)	Airway function (airway reactivity, PC30 Ln) Measured at baseline, median age 10.7 months (range 2.6–19.1)	Asthma (physician-diagnosis and report of symptoms past 12 months; use of asthma treatments) Assessed at 4 years of age	NS: OR 0.88 (0.57–1.37)	▽	Adjusted
		Measured at 1-year f/u.)		NS: OR 0.68 (0.39–1.19)	▽	
		Airway function (forced expiratory flow, z-FEF25–75) Measured at baseline, median age 10.7 months (range 2.6–19.1)		NS: OR 0.64 (0.40–1.00), *p*-value = 0.052	▽	
		Measured at 1-year f/u.)		NS: OR 1.00 (0.59–1.70)	≈	
Yao 2010[80] *n* = 114 (children)	Prospective cohort, single center (risk-enriched; increased atopy and family history of asthma; pediatric clinic)	% of conventional dendritic cells (cDCs) Measured at median age 10.7 months (range 2.6–19.1)	Wheezing episodes (phone report of symptoms) Median age inclusion for assessment 10.7 months (range 2.6–19.1), 1 year f/u	Significant: RR 0.64 (0.52–0.79)	▼	Adjusted

Note: Ages at which genetic biomarkers measured not relevant, so not included in table.

Abbreviations: CCR4, C-C chemokine receptor type 4; CI, confidence interval; FLG, filaggrin; HR, hazard ratio; IFN-γ, interferon gamma; IL, interleukin; IL10R, IL-10 receptor; IL4Rα, IL-4 receptor alpha; IR, incidence ratio; NS, not significant; NR, not reported; OR, odds ratio; PC30 Ln, natural logarithm of PC30 where PC30 is the concentration of methacholine to decrease the forced expiratory flows at 75% expired volume (FEF75) by 30%; RCT, randomized controlled trial; RR, risk ratio; SNP, single nucleotide polymorphism; SPT, skin prick test; z-FEF25–75, z-score of forced expiratory flow at 25%–75% of expired volume. ▲, presence of the biomarker is significantly associated with higher occurrence of the outcome, △, non-significantly associated with higher occurrence of the outcome, ▼, significantly associated with lower occurrence of the outcome; ▽, non-significantly associated with lower occurrence of the outcome, ≈, equivalent occurrence of outcome in those with and without the biomarker (utilized e.g., when OR = 1.0).

with s-IgE, SPTs demonstrated broadly similar results, with six studies identifying a statistically significant association between asthma and/or wheezing and sensitization to any allergen,[52,61,72] any food allergen,[29,67,72] any inhalant allergen,[29,72] egg,[67] mites,[76] and milk,[67] while no associations were found for sensitization to crab,[76] dog,[76] or cockroach[76] allergens. The age at which SPTs were performed, and at which asthma or wheezing were diagnosed ranged from 1 to 184 months and 1 to 18 years, respectively. In total seven studies examined associations with elevated total serum IgE.[29,64,66–68,75,76] Four studies reported a statistically significant association with asthma.[29,67,68,75] Two manuscripts (from a single prospective cohort) presented data on altered cytokine profiles; elevated IL-4/IFN-γ and IL-10/IFN-γ ratios at baseline predicted the later development of wheezing after 1 year follow-up, and predicted a diagnosis of asthma at 4 years of age.[68,80] The ratios of other analyzed cytokines were not associated with the development of asthma. Two studies reported data on elevated eosinophil count; demonstrating an association with the later development of asthma, albeit with varying effect size, measuring eosinophil count at different ages, and using different biomarker cut-offs.[29,75]

In total, 19 studies presented data on 26 different FLG variants individually or as a composite biomarker.[27,28,30,33,38,42,43,45,49,53,55,56,59,63,69,76,77,79,81] Results were inconsistent. Overall, 16 out of the 36 presented FLG-related outcomes demonstrated significant associations with asthma[28,33,45,49,53,55,56,69,76,77,81] and wheezing.[33] Two studies reported the relationship between asthma and the FLG P478S polymorphism (rs11584340), frequently identified among Chinese individuals.[76,77] Margolis et al.[59] reported

TABLE 2 Overview: Studies evaluating biomarkers predictive of food allergies and adverse food reactions

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result measures of effect (95% CI)	Result summary	Analysis
Allergen specific IgE (co, cod; e, egg; m, milk; p, peanut; s, soy; wh, wheat)						
Gustafsson 2000[40] *n* = 94 (children)	Prospective cohort, multicenter (allergy clinic or child welfare clinic)	Food (co, e, m, s, wh) Measured before 36 months of age	Adverse food reactions (NR) Assessed between 5–8 years of age	Significant: OR 4.2 (1.7–10.6)	▲	Crude
Spergel 2015[70] *n* = 1065 (children)	RCT/prospective cohort, multi-center (clinics; family history of atopy)	Cow's milk	Corresponding food allergy (Thompson and Hanifin criteria – points-based symptom criteria) Age of assessment NR, >3 years f/u	Significant: OR 1.88 (1.61–2.19)	▲	Crude
		Egg white		Significant: OR 1.44 (1.26–1.66)	▲	
		Peanut		Significant: OR 1.58 (1.41–1.78)	▲	
		Seafood mix		Significant: OR 2.78 (1.49–5.20)	▲	
		Wheat		NS: OR 1.33 (0.77–2.32)	△	
		Soybean Measured at mean age 7.3 (±3.9) months of age		NS: OR 1.73 (1.00–3.01), *p*-value = 0.052	△	
SPT (al, alternaria; c, cat; coc, cockroach; e, egg; hdm, house dust mites; p, peanut; s, soy)						
Du Toit 2015[31] *n* = 628 (children)	RCT/prospective cohort, single center (children's hospital)	Peanut Measured at mean age 7.8 (±1.71) months	Peanut allergy (oral peanut challenge in 96% and clinical algorithm in 4% of participants) Assessed at 60 months of age	Significant: OR 3.81 (2.16–6.72)	▲	Crude
Tran 2018[72] *n* = 266 (children)	Prospective birth cohort, multicenter (population-based)	Food (e, m, p, s)	Food allergy (physician diagnosis based on clinical history) Assessed at 3 years of age	Significant: RR 14.3 (6.10–33.4)	▲	Adjusted
		Inhalant (al, c, coc, d, hdm)		NS: RR 1.19 (0.53–2.67)	△	
		Any (al, c, coc, d, e, hdm, p, s) Measured at 1 year of age		Significant: RR 14.0 (5.71–34.4)	▲	
FLG and other skin barrier genetic variants						
Filipiak Pittroff 2011[33] *n* = 65 (children)	Prospective cohort, multicenter (risk-enriched sample; 50% with known food allergy)	R501X, 2282del4, R2447X, or S3247X	Food allergy (symptoms, s-IgE and double-blind, placebo-controlled food challenges) Mean age at assessment NR, 8 year f/u	NS: OR 0.67 (0.22–2.06)	▽	Crude
Heede 2017[42] *n* = 225 (adults)	Cross-sectional study, single center (dermatology department)	R501X, 2282del14, or R2447X	Food allergies (self-reported lifetime prevalence of doctor's diagnosis) Assessed at median age of 42 years	NS: OR 1.01 (0.55–1.83)	△	Crude
Margolis 2019[59] *n* = NR (children)	Prospective cohort, multicenter (secondary and primary care)	24 FLG variants	Food allergies (NR) Age at assessment NR	Significant: OR 1.82 (1.29–2.59)	▲	Crude
Hertz 2020[44] *n* = 43 (adults/children)	Cross-sectional study, multicenter (dermatology outpatient departments)	FLG-2 variants (rs16833974, rs12568784)	Food allergies (NR) Age at assessment between 1–27 years of age	NS: rs16833974 OR 0.29 (0.03–2.77)	▽	Crude
				NS: rs12568784 OR 0.75 (0.21–2.66)	▽	

(Continues)

TABLE 2 (Continued)

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result measures of effect (95% CI)	Result summary	Analysis
Margolis 2014[57] *n* = 299 (African American children)	Prospective cohort, multicenter (secondary and primary care)	FLG-2 variants (rs12568784, rs150529054, Q2053del224)	Food allergies (NR) Assessed at mean age 6.8 (±NR) years	NS: rs12568784 OR 0.96 (0.84–1.11)	▽	Crude
				NS: rs150529054 OR 0.79 (0.42–1.47)	▽	
				NS: Q2053del224 OR 1.42 (0.71–2.81)	△	
Other genetic variants						
Potaczek 2011[65] *n* = 130 (adults, unclear if also includes children)	Cross-sectional study, (setting unclear)	TLR2-16934 A>T polymorphism (A allele)	Food allergies (diagnosis based on medical history, physical examination, total serum IgE levels and positive intracutaneous skin tests) Assessed at mean age 29.6 (±0.98) years	NS: overall OR 1.59 (0.61–4.17)	△	Crude
				NS: stratified by IgE ≥ 106: OR 1.87 (0.44–7.87)	△	
				NS: stratified by IgE < 106: OR 1.39 (0.38–5.09)	△	
		TLR2-16934 A>T polymorphism (AA genotype)		NS: overall OR 0.54 (0.22–1.27)	▽	
				NS: stratified by IgE ≥ 106: OR 0.43 (0.12–1.55)	▽	
				NS: stratified by IgE < 106: OR 0.65 (0.20–2.11)	▽	
Other biomarkers						
Tsilochristou 2019[73] *n* = 628 (children)	RCT/prospective cohort, single center (children's hospital)	*Staphylococcus aureus* colonization – nasal	Peanut allergy (oral peanut challenge in 96% and clinical algorithm in 4% of participants) Assessed at 72 months of age	Significant: OR 2.18 (1.05–4.56)	▲	Adjusted
		S. aureus colonization – skin		Significant: OR 2.19 (1.04–4.61)	▲	
		S. aureus colonization - skin and/or nasal Measured at baseline, 12, 30, 60 months of age		Significant: OR 2.78 (1.09–7.07)	▲	

Note: Ages at which genetic biomarkers measured not relevant, so not included in table.

Abbreviations: CI, confidence interval; FLG, filaggrin; f/u, follow-up; NR, not reported; NS, not significant; OR, odds ratio; RCT, randomized controlled trial; RR, risk ratio; SPT, skin prick test; TLR2, toll-like receptors. ▲, presence of the biomarker is significantly associated with higher occurrence of the outcome; △, non-significantly associated with higher occurrence of the outcome; ▼, significantly associated with lower occurrence of the outcome; ▽, non-significantly associated with lower occurrence of the outcome, ≈, equivalent occurrence of outcome in those with and without the biomarker (utilized e.g. when OR = 1.0).

on the association of FLG LOF mutations and asthma in an ethnically diverse cohort (44% African American), while the other outcomes related to R501X, 2282del4, R2447X, and S3247X individually or as a composite biomarker in Caucasian cohorts.[28,33,45,49,53,55,56,69,81] FLG-2 variants were evaluated in two studies.[44,57] Seven studies investigated other genetic variants, including thymic stromal lymphopoietin (TSLP), toll-like receptor-2 (TLR2) and interleukin (IL) receptor gene polymorphisms.[28,39,47,54,58,65,74] Significant associations were also identified for rs7927894 (chromosome 11q13 polymorphism) and TLR2-16934 A>T polymorphisms, while a C-C chemokine receptor type 4 (CCR4) gene polymorphism was found to be protective against the development of asthma among Japanese individuals.[54,65,74] The combination of FLG mutations and sensitization to food allergens (assessed with s-IgE before 3 years of age) was evaluated in three cohorts; overall there were positive associations between this composite biomarker and the development of asthma and/or wheezing in childhood, although the statistical significance of these findings varied by cohort.[33,55] Similarly, the combination of FLG P478S TT genotype and house dust mite sensitization (assessed using SPT at 3 years of age) was associated with asthma at age 6.[76] Pulmonary function and airway reactivity were studied in one cohort, but the findings were not statistically significant.[68]

3.3.2 | Food allergy and adverse food reactions

Eleven articles reported results from nine different cohorts investigating the association between candidate biomarkers and the development of food allergies and adverse food reactions (Table 2). Two studies examined elevated s-IgE.[40,70] Gustafsson et al.[40] reported an association between sensitization to any food allergen before 3 years of age and the later development of adverse food reactions (assessed between 5 and 8 years of age), while Spergel et al.[70] presented data on s-IgE to individual food allergens measured at mean age 7.2 (±3.9) months, and the association with clinically-diagnosed food allergy after at least 3 years of follow-up (before 6 years of age). Both studies reported significant associations between sensitization and later development of food allergy, and Spergel et al. demonstrated significant associations between cow's milk, egg white, peanut, and seafood mix and the corresponding food allergy, but not for wheat or soybean. Two studies reported outcomes on sensitization assessed by SPTs.[31,72] They found associations between positive SPTs to any allergens, one or more food allergens[72] and peanut allergens[31] and food allergy, but not for any inhalant allergens.[72]

Five studies investigated FLG or FLG-2 mutations.[33,42,44,57,59] One of these studies reported a significant association for carrying any of 24 FLG variants.[59] The other 3 studies found no associations between FLG LOF mutations (R501X, 2282del4, R2447X, or S3247X composite,[33] or R501X, 2282del14, or R2447X composite[42]) or FLG-2 variants (rs16833974, rs12568784, rs150529054, Q2053del224 individually) and food allergies.[44,57] Potaczek et al.[65] examined TLR2-16934 A>T polymorphism (A allele, AA genotype) and found no association with the presence of food allergies. One study investigated *Staphylococcus aureus* colonization of the skin and/or nares, and found a significant association between being colonized at either body site and the subsequent development of peanut allergy.[73]

3.3.3 | Allergic rhinoconjunctivitis and related conditions

Twenty-three studies reported results from 24 cohorts investigating the association between candidate biomarkers and allergic rhinitis, allergic conjunctivitis, allergic rhinoconjunctivitis (hay fever), and seasonal allergies (Table 3). For simplicity, these related and interchangeable conditions will be described as allergic rhinoconjunctivitis (AR) hereafter.

Six studies, reporting on seven separate cohorts, evaluated the associations between AR and elevated s-IgE to food allergens, inhalant allergens, or either food or inhalant allergens.[26,29,33,40,66,67] The age at which biomarkers were measured ranged from 1 to 96 months, and the age at which AR was diagnosed range from 5 to 20 years of age. Sensitization to inhalant allergens was associated with later diagnosis of AR in two of three cohorts,[26,29,33,40,66,67] while sensitization to food allergens was associated with subsequent AR in two of six cohorts.[32,39] Studies evaluating the predictive role of SPTs used varying study designs, and assessed sensitization between 1 and 184 months of age, and diagnosed AR after 2 to 7.5 years follow-up.[29,52,64,67,72] Results were conflicting for inhalant allergens, food allergens, and the combination of inhalant and food allergens. There was a positive association between elevated total IgE in two studies,[29,66] while one study evaluated the development of either asthma or AR, and found no association with total IgE levels.[64] The single study evaluating eosinophil count as a biomarker for AR demonstrated a statistically significant result.[29]

Filaggrin and FLG-2 LOF mutations were assessed in 11 studies. Mutation carriers were, in general, not at significantly greater risk of developing AR than patients with FLG wild-type.[28,33,42,45,53,57,59,69,77,79,81] In total 5 studies assessed other genetic variants and found significant associations between rs7927894 (T risk allele)[54] and TLR2-16934 A>T polymorphism (A allele or AA genotype)[65] and AR.

3.3.4 | Other allergic conditions

Eight cohorts investigated the association between candidate biomarkers and other allergic conditions, including urticaria, allergic contact dermatitis (ACD), hand eczema, animal allergies, and drug allergies (Table 4). A single study reported a significant association between elevated s-IgE to any food allergens (before 36 months of age) and the development of urticaria (diagnosed between 3 and 8 years of age based on typical symptoms).[40] However, it was not clear if the authors were reporting spontaneous and/or induced urticaria, nor whether the urticaria was related to food exposures. Hand eczema was not consistently predicted by FLG status.[41,42,45,53,71] ACD was investigated in two cohorts, and no association with FLG status or other genetic biomarkers (SPINK5, KLK7, and immune response-related genes) was identified.[48,71] Allergies to animals were significantly associated with a panel of 24 FLG variants, while allergies to medications were not.[59]

3.3.5 | Cutaneous viral infection

Eight studies reported results from three cohorts which investigated candidate biomarkers to predict eczema herpeticum (EH) and/or a history of herpes simplex virus (HSV) infection (Table 5). The FLG R501X mutation was significantly associated with susceptibility to EH in both a European American and an African American population.[36] FLG polymorphism rs1933063 was associated with statistically lower odds of EH in European Americans, but there was no statistically significant protective effect found in African Americans.[36] In African Americans, but not European Americans, FLG rs2065956 was significantly associated with EH.[36] In a Finnish cohort, an association between FLG R501X and HSV symptoms approached statistical significance (OR 3.80; 95%

TABLE 3 Overview: Studies evaluating biomarkers predictive of allergic rhinoconjunctivitis (hay fever), allergic rhinitis, allergic conjunctivitis, and seasonal allergies

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result measures of effect (95% CI)	Result summary	Analysis
Allergen specific IgE (α, α-lactalbumin; ahf, animal hair-fur; β, β-lactoglobulin; b, birch; c, cat; ca, casein; co, cod; d, dog; e, egg; f, fish; fl, flour; g, grass; h, horse; hd, house dust; hdm, house dust mites; mu, mugwort; p, peanut; s, soy; t, timothy grass; w, weed; wh, wheat)						
Ballardini 2014[26] *n* = 137 (children)	Prospective birth cohort, multicenter (population-based)	Any (b, c, co, d, e, h, hdm, mu, p, s, wh) Measured at 2 years of age	Rhinitis (questionnaire report of symptoms, or doctor's diagnosis) Assessed at 12 years of age	Significant: OR 4.32 (2.04–9.12)	▲	Adjusted
Cosickic 2017[29] *n* = 114 (children)	Prospective cohort, single center (pediatric department)	Food (e, m, f, fl, p, s) Inhalant (ahf, hd, hdm, g, w) Measured at median age 26.5 (range 1.5–96) months and yearly over 5 years	Rhinitis (questionnaire report of symptoms) Assessed between 5.1–13 years of age	NS: OR 1.45 (0.6–3.3) Significant: OR 13.2 (4.5–38.9)	△ ▲	Crude
Filipiak Pittroff 2011[33] *n* = 235 (children)	Prospective birth cohort, multicenter (population-based)	Food (e, co, m, p, s, wh)	Rhinitis (questionnaire report of symptoms) Assessed at 10 years of age	Significant: OR 2.55 (1.09–5.98)	▲	Crude
Filipiak Pittroff 2011[33] *n* = 183 (children)	RCT/prospective birth cohort, multicenter (risk-enriched sample; family history of allergic disease)	Food (α, β, ca, e, s) Measured at 2 years of age	Rhinitis (questionnaire report of symptoms) Assessed at 10 years of age	NS: OR 1.81 (0.86–3.79)	△	Crude
Gustafsson 2000[40] *n* = 94 (children)	Prospective cohort, multicenter (allergy clinic or child welfare clinic)	Food (co, e, m, s, wh) Measured <36 months of age	Allergic eye-nose symptoms (report of symptoms) Assessed between 5–8 years of age	Significant: OR 8.9 (3.2–24.7)	▲	Crude
Ricci 2006[66] *n* = 205 (children and adolescents)	Retrospective cohort with a prospective follow-up interview, single center (tertiary center)	Egg Cow's milk Inhalant (al, c, d, g, h, hdm) Measured at 6–36 months of age	Rhinoconjunctivitis (questionnaire and medical records) Age inclusion for assessment between 6–36 months, mean 16.9 year f/u	NS: OR 1.95 (1.00–3.80), *p*-value = 0.051 NS: OR 1.97 (0.89–4.36) Significant: OR 2.40 (1.18–4.88)	△ △ ▲	Crude
Ricci 2010[67] *n* = 176 (children)	Retrospective cohort with a prospective follow-up interview, single center (tertiary center)	Egg Cow's milk Food (a, co, e, m, n, p, s, wh) Inhalant (al, c, d, g, hdm) Measured at mean age 11.7 (±NR) months	Rhinoconjunctivitis (diagnosed by GP or pediatric allergist/pulmonologist) Mean age inclusion for assessment 11.7 (±NR) months, mean 7.5 year f/u	NS: OR 0.94 (0.48–1.83) NS: OR 0.98 (0.50–1.92) NS: OR 0.88 (0.45–1.72) NS: OR 1.22 (0.55–2.73)	▽ ▽ ▽ △	Crude

TABLE 3 (Continued)

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result measures of effect (95% CI)	Result summary	Analysis
SPT (ahf, animal hair-fur; al, alternaria; b, bacteria; c, cat; co, cod; coc, cockroach; cs, cupressus semprecires; e, egg; fa, fabrics; fe, feathers; fl, flour; fr, fuit; fu, fungi; m, milk; me, meat; mu, mugwort; hd, house dust; hdm, house dust mite; h, hazel; o, olive tree; p, peanut; pa, parietaria; po, poplar; to, tomato; tr, tree; v, vegetables; w, weed; wh, wheat)						
Cosickic 2017[29] *n* = 114 (children)	Prospective cohort, single center (pediatric department)	Food (e, m, fl, me l and II, fr I, II and III, v I and II)	Rhinitis (questionnaire report of symptoms) Assessed between 5.1–13 years of age	Significant: OR 9.9 (3.5–22.9)	▲	Crude
		Inhalant (ahf, b, fa, fe, fu, g, hd, hdm, tr, w, v) Measured at median age 26.5 (range 1.5–96) months and yearly over 5 years		Significant: OR 3.6 (1.5–8.2)	▲	
Lowe 2007[52] *n* = 189 (children)	Prospective birth cohort, single center (risk-enriched sample; family history of atopy)	Any (c, e, g, hdm, m, p) Measured at 6 months, 1 year, 2 years of age	Rhinitis (physician-diagnosed and treated with antihistamine and/or nasal steroid) Assessed between 6–7 years of age	Significant: OR 2.61 (1.28–5.30)	▲	Adjusted
Piancatelli 2008[64] *n* = 27 (children)	Prospective cohort, single center (setting unclear)	Any (al, c, e, h, hdm, m, mu, o, po, w) Measured between 1–184 months of age	Asthma or rhinoconjunctivitis (NR) Age range inclusion for assessment between 1–184 months, 3 years f/u	NS: OR 11.9 (0.59–237.4)	△	Crude
Ricci 2010[67] *n* = 176 (children)	Retrospective cohort with a prospective follow-up interview, single center (tertiary center)	Egg	Rhinoconjunctivitis (diagnosed by GP or pediatric allergist/pulmonologist) Mean age inclusion for assessment 11.7 (±NR) months, mean 7.5 years f/u	NS: OR 0.94 (0.48–1.83)	▽	Crude
		Cow's milk		NS: OR 0.99 (0.47–2.08)	▽	
		Food (a, co, e, m, n, p, s, wh)		NS: OR 0.95 (0.49–1.85)	▽	
		Inhalant (al, c, d, g, hdm) Measured at mean age 11.7 (±NR) months		Significant: OR 3.47 (1.10–10.92)	▲	
Tran 2018[72] *n* = 265 (children)	Prospective birth cohort, multicenter (population-based)	Food (e, m, p, s)	Allergic rhinitis (physician diagnosis based on clinical history) Assessed at 3 years of age	NS: RR 1.68 (0.61–4.64)	△	Adjusted
		Inhalant (al, c, coc, d, hdm)		NS: RR 3.84 (0.90–16.3)	△	
		Any (al, c, coc, d, e, hdm, p, s) Measured at 1 year of age		NS: RR 1.87 (0.78–4.49)	△	
Total serum IgE						
Cosickic 2017[29] *n* = 114 (children)	Prospective cohort, single center (pediatric department)	Total serum IgE >100 IU/mL Measured at median age 26.5 (range 1.5–96) months and yearly over 5 years	Rhinitis (questionnaire report of symptoms) Assessed between 5.1–13 years of age	Significant: OR 4.2 (1.6–10.8)	▲	Crude

(Continues)

TABLE 3 (Continued)

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result measures of effect (95% CI)	Result summary	Analysis
Piancatelli 2008[64] *n* = 27 (children)	Prospective cohort, single center (setting unclear)	Total serum IgE Age-specific reference ranges [U/ml]: (2–5 years, >60; 6–9 years, >75;10–13 years, >155; >13 years, >I00) Measured between 1–184 months of age	Asthma or rhinoconjunctivitis (NR) Age range inclusion for assessment between 1–184 months, 3 years f/u	NS: OR 8.0 (0.82–77.8)	△	Crude
Ricci 2006[66] *n* = 205 (children and adolescents)	Retrospective cohort with a prospective follow-up interview, single center (tertiary center)	Total serum IgE age-specific (NR) Measured at 6–36 months of age	Rhinoconjunctivitis (questionnaire and medical records) Age inclusion for assessment between 6–36 months, mean 16.9 years f/u	Significant: OR 1.76 (1.00–3.08), *p*-value = 0.049	▲	Crude
Eosinophils						
Cosickic 2017[29] *n* = 114 (children)	Prospective cohort, single center (pediatric department)	Eosinophils count ≥0.45 x 10^9/L Measured at median age 26.5 (range 1.5–96) months and yearly over 5 years	Rhinitis (questionnaire report of symptoms) Assessed between 5.1–13 years of age	Significant: OR 11.1 (4.3–32.5)	▲	Crude
FLG and other skin barrier genetic variants						
Chang 2017[28] *n* = 842 (children)	Prospective cohort, multicenter (secondary and primary care)	R501X, 2282del4, R2447X, or S3247X	Seasonal allergies (NR) Assessed at mean age 7.2 (±3.8) years	NS: OR 1.24 (0.83–1.85)	△	Crude
Filipiak Pittroff 2011[33] *n* = 137 (children)	RCT/prospective birth cohort, multicenter (risk-enriched sample; family history of allergic disease)	R501X or 2282del4	Rhinitis (questionnaire report of symptoms) Assessed at 10 years of age	NS: OR 1.20 (0.42–3.42)	△	Crude
Filipiak Pittroff 2011[33] *n* = 145 (children)	Prospective birth cohort, multicenter (population-based)		Rhinitis (questionnaire report of symptoms) Assessed at 10 years of age	NS: OR 1.61 (0.47–5.48)	△	Crude
Filipiak Pittroff 2011[33] *n* = 65 (children)	Prospective cohort, multicenter (risk-enriched sample; 50% with known food allergy)		Rhinitis (parental report of physician-diagnosis) Age at assessment NR, mean 8 years f/u	NS: OR 2.72 (0.92–8.03)	△	Crude
Heede 2017[42] *n* = 227 (adults)	Cross-sectional study, single center (dermatology department)	R501X, 2282del4, or R2447X	Rhinitis (self-reported lifetime prevalence of doctor's diagnosis) Assessed at median age of 42 years	NS: OR 1.31 (0.72–2.39)	△	Crude

TABLE 3 (Continued)

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result measures of effect (95% CI)	Result summary	Analysis
Holm 2019[45] *n* = 141 (adults/children)	Cross-sectional study, single center (dermatology outpatient department)	R501X, 2282del4, or R2447X	Rhinoconjunctivitis (early-onset) (questionnaire report of symptoms) Assessed at mean age 18.7 (±16.5) years	NS: OR 1.17 (0.55–2.46)	△	Crude
n = 153 (adults/children)			Rhinoconjunctivitis (late-onset) (questionnaire report of symptoms) Assessed at mean age 18.7 (±16.5) years	NS: OR 0.93 (0.43–2.05)	▽	
Luukkonen 2017[53] *n* = 438 (adults/children)	Prospective cohort, single center (skin and allergy hospital)	R501X	Allergic conjunctivitis (NR) Mean age inclusion for assessment 32.3 (±14.9) years, 1 year f/u	NS: OR 0.74 (0.17–3.15)	▽	Crude
		2282del4		NS: OR 1.22 (0.53–2.82)	△	
		R2447X		NS: OR 2.00 (0.43–9.40)	△	
		R501X, 2282del4, or R2447X		NS: OR 1.33 (0.67–2.65)	△	
		R501X	Allergic rhinitis (NR) Mean age inclusion for assessment 32.3 (±14.9) years, 1 year f/u	NS: OR 5.23 (0.30–91.47)	△	
		2282del4		NS: OR 0.84 (0.36–1.96)	▽	
		R2447X		NS: OR 3.06 (0.39–24.23)	△	
		R501X, 2282del4, or R2447X		NS: OR 1.33 (0.62–2.8)	△	
Margolis 2019[59] *n* = NR (children)	Prospective cohort, multicenter (secondary and primary care)	24 FLG variants	Seasonal allergies (NR) Age at assessment NR	NS: OR 1.20 (0.82–1.75)	△	Crude
Schuttelaar 2009[69] *n* = NR (children)	Prospective birth cohort, multicenter (risk-enriched, 67% of mothers were allergic; midwifery practices)	2282del4	Hay fever (NR) Assessed between 6–8 years of age	Significant: OR 4.0 (1.2–13.6)	▲	Crude
Wang 2011[77] *n* = 116 (children)	Cross-sectional study multicenter (hospital-based clinics)	P478S polymorphism (rs11584340)	Rhinitis (parental report of doctor's diagnosis) Age at assessment NR	Significant: OR 3.23 (1.01–10.30)	▲	Crude
Weidinger 2008[79] *n* = 540 (children)	Cross-sectional study within prospective cohort study, multicenter (community-based)	R501X, 2282del4, or 3702delG	Allergic rhinitis (parent-report of doctor's diagnosis plus positive SPT, NR for AD group) Assessed at mean age 9.6 (±0.6) years in overall study population	Significant: OR 2.00 (1.08–3.18)	▲	Crude

(Continues)

TABLE 3 (Continued)

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result measures of effect (95% CI)	Result summary	Analysis
Ziyab 2014[81] *n* = NR (Overall: *k* = 576, *k* = 181 with rhinitis; Sensitized: *k* = 210, *k* = 100 with rhinitis; Non-sensitized: *k* = 290, *k* = 68 with rhinitis, children)	Prospective birth cohort, multicenter (population-based)	R501X, 2282del4, or S3247X	Rhinitis (questionnaire report of symptoms) Assessed between 1–18 years of age	Significant: RR 1.57 (1.23–2.00) Significant: sensitized: RR 1.44 (1.10–1.88) NS: non-sensitized: RR 1.20 (0.62–2.34)	▲ ▲ △	Adjusted
Margolis 2014[57] *n* = 299 (African American children)	Prospective cohort, multicenter (secondary and primary care)	FLG-2 variants (rs12568784, rs150529054, Q2053del224)	Seasonal allergies (NR) Assessed at mean age 6.8 (±NR) years	NS: rs12568784 OR 1.01 (0.66–1.56) NS: rs150529054 OR 0.89 (0.48–1.44) NS: Q2053del224 OR 0.58 (0.23–1.52)	△ ▽ ▽	Crude
TSLP genetic variants						
Chang 2017[28] *n* = 770 (children)	Prospective cohort, multicenter (secondary and primary care)	TSLP SNP - rs1898671	Seasonal allergies (NR) Assessed at mean age 7.2 (±3.8) years	NS: OR 1.05 (0.77–1.43)	△	Crude
Other genetic variants						
Greisenegger 2013[39] *n* = 251 (adults)	Cross-sectional study, multicenter (allergy or dermatology outpatient clinics)	HRNR gene- rs877776 rs7927894 (chromosome 11q13 SNP)	Rhinoconjunctivitis (NR) Assessed at median age 28 years	NS: OR and CI NR NS: OR 1.03 (0.59–1.80)	NR △	Adjusted
Kayserova 2012[47] *n* = 74 (children)	Prospective cohort, multicenter (dermatology and immunology departments)	IL10R gene polymorphism	Rhinitis (clinical manifestations) Assessed between 0–3 years of age	NS: -1082A/G: *p*-value = 0.241 NS: -819C/T: *p*-value = 0.085 NS: -529A/C: *p*-value = 0.083	≈ △ (TT genotype) △ (AA genotype)	Crude
		IL4Rα gene polymorphism		NS: +1902A/G: *p*-value = 0.536	≈	
Marenholz 2011[54] *n* = 757 (children)	Cross-sectional study, multicenter (family-based association)	rs7927894 (T risk allele) (chromosome 11q13 SNP)	Hay fever (parent report of doctor-diagnosis) Assessed at mean age 7.9 (±NR) years	Significant: OR 1.41 (1.13–1.74)	▲	Crude
Marenholz 2011[54] *n* = 1120 (children)	Prospective birth cohort, multicenter (population-based)	rs7927894 (T risk allele) (chromosome 11q13 SNP)	Hay fever (questionnaire report) Assessed at 13 years of age	Significant: OR 1.23 (1.01–1.49)	▲	Adjusted

TABLE 3 (Continued)

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result measures of effect (95% CI)	Result summary	Analysis
Potaczek 2011[65] *n* = 130 (adults, unclear if also includes children)	Cross-sectional study, (setting unclear)	TLR2-16934 A>T polymorphism (A allele)	Allergic conjunctivitis (NR) Assessed at mean age 29.6 (±0.98) years	NS: overall OR 2.91 (0.93–9.14)	△	Crude
				Significant: stratified by IgE ≥106 OR 20.5 (1.15–366.3)	▲	
				NS: stratified by IgE <106 OR 0.84 (0.23–3.15)	▽	
			Allergic rhinitis (diagnosis based on medical history, physical examination, total serum IgE levels and positive intracutaneous skin tests) Assessed at mean age 29.6 (±0.98) years	NS: OR 1.04 (0.43–2.52)	△	
				NS: stratified by IgE ≥106: OR 1.67 (0.44–6.25)	△	
				NS: stratified by IgE <106: OR 0.67 (0.20–2.26)	▽	
		TLR2-16934 A>T polymorphism (AA genotype)	Allergic conjunctivitis (NR) Assessed at mean age 29.6 (±0.98) years	NS: OR 1.45 (0.64–3.30)	△	
				NS: stratified by IgE ≥106: OR 2.66 (0.83–8.51)	△	
				NS: stratified by IgE <106: OR 0.78 (0.22–2.84)	▽	
			Allergic rhinitis (diagnosis based on medical history, physical examination, total serum IgE levels and positive intracutaneous skin tests) Assessed at mean age 29.6 (±0.98) years	NS: OR 1.04 (0.47–2.29)	△	
				NS: stratified by IgE ≥106: OR 0.89 (0.27–2.89)	▽	
				NS: stratified by IgE <106: OR 1.18 (0.38–3.61)	△	

Note: Ages at which genetic biomarkers measured not relevant, so not included in table.

Abbreviations: CI, confidence interval; f/u, follow-up; FLG, filaggrin; HR, hazard ratio; HRNR, hornerin; IFN-γ, interferon gamma; IL, interleukin; IL-10 receptor; IL10R; IL4Rα, IL-4 receptor alpha; NR, not reported; NS, not significant; OR, odds ratio; RCT, randomized controlled trial; RR, risk ratio; SNP, single nucleotide polymorphism; SPT, skin prick test; TLR2, toll-like receptors; TSLP, thymic stromal lymphopoietin; ▲, presence of the biomarker is significantly associated with higher occurrence of the outcome; △, non-significantly associated with higher occurrence of the outcome; ▼, significantly associated with lower occurrence of the outcome; ▽, non-significantly associated with lower occurrence of the outcome; ≈, equivalent occurrence of outcome in those with and without the biomarker (utilized e.g. when OR = 1.0).

k = number of repeated measurements.

CI 0.89 to 16.16, $p = 0.07$), but the association with FLG R2447X and with FLG 2282del4, as well as the association of HSV symptoms with any of these three FLG mutations was conflicting.[53] Three studies investigated other genetic biomarkers (TSLP,[37] TSLPR,[37] IL7R,[37] STAT6,[46] and MHC (major histocompatibility complex) class I alleles[60]), with results demonstrating significant genotype–phenotype variability, with different TSLP, IRF2, IL7R, STAT6 alleles conferring opposing (protective and predisposing) effects. Three studies assessed interferon-related genetic variants, with the majority of variants conferring a significantly protective effect for EH.[34,35,50]

3.3.6 | Other comorbidities, including ichthyosis, neuropsychiatric disorders, and malignancies

A single cohort investigated the association between FLG variants (individually or as a composite marker) with ichthyosis vulgaris in patients with AD.[32] Significant associations were reported for 2 of the 3 investigated biomarkers, namely between 2282del4, and the presence of either R501X or 2282del4 variants and ichthyosis vulgaris.[32] There was no association between R501X and ichthyosis. A small, single-center Danish cohort investigated for associations between FLG mutation status and self-reported comorbidities, and identified

TABLE 4 Overview: Studies evaluating biomarkers predictive of other allergic conditions

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result measures of effect (95% CI)	Result summary	Analysis
Allergen specific IgE (co, cod; e, egg; m, milk; p, peanut; s, soy; wh, wheat)						
Gustafsson 2000[40] *n* = 94 (children)	Prospective cohort, multicenter (allergy clinic or child welfare clinic)	Food (co, e, m, p, s, wh) Measured before36 months age	Urticaria (report of symptoms, not defined if spontaneous or induced, or related to food triggers) Assessed between 5–8 years of age	Significant: OR 7.5 (2.8–20.1)	▲	Crude
FLG and other skin barrier genetic variants						
Heede 2015[41] *n* = 199 (adults)	Prospective cohort, multicenter (population-based)	R501X, 2282del4, or R2447X	Hand eczema (self-reported; persistent or occasional symptoms) Mean age inclusion for assessment in overall study population 50 years, over 5 years f/u	Significant: OR 3.51 (1.67–7.38)	▲	Crude
Heede 2017[42] *n* = 228 (adults)	Cross-sectional study, single center (dermatology department)	R501X, 2282del4, or R2447X	Hand eczema current (clinical diagnosis) Assessed at median age of 42 years	Significant: OR 2.11 (1.13–3.95)	▲	Crude
n = 230 (adults)			Hand eczema ever (self-report) Assessed at median age of 42 years	NS: OR 1.87 (0.73–4.75)	△	
Holm 2019[45] *n* = 141 (adults/children)	Cross-sectional study, single center (dermatology outpatient department)	R501X, 2282del4, or R2447X	Hand eczema (early-onset, questionnaire report of symptoms) Assessed at mean age 18.7 (±16.5) years	NS: OR 1.27 (0.51–3.12)	△	Crude
n = 153 (adults/children)			Hand eczema (late-onset, questionnaire report of symptoms) Assessed at mean age 18.7 (±16.5) years	NS: OR 0.90 (0.38–2.08)	▽	
Luukkonen 2017[53] *n* = 4311 (adults/children)	Prospective cohort, single center (skin and allergy hospital)	R501X 2282del4 R2447X R501X, 2282del4, or R2447X	Hand eczema (NR) Mean age inclusion for assessment 32.3 (±14.9) years, 1 year f/u	NS: OR 1.59 (0.19–13.4) NS: OR 0.62 (0.27–1.40) NS: OR 0.62 (0.16–2.45) NS: OR 0.67 (0.34–1.34)	△ ▽ ▽ ▽	Crude
Thyssen 2010[71] *n* = NR (adults)	Cross-sectional study, single center (population-based)	R501X or 2282del4	Hand eczema ever (self-report, questionnaire self-report) Assessed between 18–69 years	NS: OR 1.28 (0.70–2.33)	△	Crude
			Hand eczema recent (past 12 months, questionnaire self-report) Assessed between 18–69 years	Significant: OR 2.98 (1.27–7.01)	▲	Adjusted
			Contact allergy (diagnosed by patch-testing) Assessed between 18–69 years	NS: OR 1.36 (0.63–2.94)	△	Crude

TABLE 4 (Continued)

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result measures of effect (95% CI)	Result summary	Analysis
Lee 2018[48] *n* = 281 (adults/children)	Cross-sectional study, single center (outpatient dermatology department)	3321delA	Allergic contact dermatitis (diagnosed by patch testing) Assessed at mean age 17.1 (±16.3) years	NS: OR 1.78 (0.61–4.81)	△	Adjusted
		K4022X		NS: OR 0.79 (0.19–2.68)	▽	
		SPINK5 variants		NS: G1156A HTZ: OR 1.0 (0.53–1.86)	≈	
				NS: G1156A HMZ: OR 1.09 (0.13–5.98)	△	
				NS: C1188T HTZ: OR 0.70 (0.35–1.41)	▽	
				NS: C1188T HMZ: OR 0.51 (0.19–1.25)	▽	
				NS: G2475T HTZ: OR 1.56 (0.82–2.99)	△	
				NS: G2475T HMZ: OR 1.09 (0.38–2.84)	△	
		KLK7 variant		NS: HTZ: OR 0.75 (0.39–1.44)	▽	
				NS: HMZ: OR 0.89 (0.32–2.32)	▽	
Margolis 2019[59] *n* = NR (children)	Prospective cohort, multicenter (secondary and primary care)	24 FLG variants (composite)	Animal allergies (NR) Age at assessment NR	Significant: OR 1.90 (1.34–2.71)	▲	Crude
			Medication allergies (NR) Age at assessment NR	NS: OR 1.54 (0.999–2.39)	△	
Other genetic variants						
Lee 2018[48] *n* = 281 (adults/children)	Cross-sectional study, single center (outpatient dermatology department)	Immune-response-related variants	Allergic contact dermatitis (diagnosed by patch testing) Assessed at mean age 17.1 (±16.3) years	NS: DFB1 C2266T HTZ: OR 1.55 (0.73–3.48)	△	Adjusted
				NS: DFB1 C2266T HMZ: OR 11.98 (0.61–6.01)	△	
				NS: KDR HTZ: OR 0.99 (0.47–2.01)	▽	
				NS: IL5RA HTZ: OR 0.73 (0.40–1.33)	▽	
				NS: IL-9 HTZ: OR 1.66 (0.88–3.15)	△	
				NS: IL-9 HMZ: OR 5.38 (0.17–174.84)	△	
				NS: IL12RB1-a HTZ: OR 1.17 (0.64–2.17)	△	
				NS: IL12RB1-b HTZ: OR 0.60 (0.29–1.17)	▽	
				NS: IL12RB1-b HMZ: OR 1.78 (0.33–8.19)	△	

Note: Ages at which genetic biomarkers measured not relevant, so not included in table.

Abbreviations: CI, confidence interval; DFB1, Nonsyndromic hearing loss and deafness; f/u, follow-up; HMZ, homozygous; HTZ, heterozygous; IL, interleukin; IL12RB1, IL-12 receptor, beta 1; IL5RA, IL-5 receptor alpha; KDR, kinase insert domain receptor; KLK7, kallikrein related peptidase 7; NR, not reported; OR, odds ratio; SPINK5, serine peptidase inhibitor Kazal type 5; ▲, presence of the biomarker is significantly associated with higher occurrence of the outcome; △, non-significantly associated with higher occurrence of the outcome; ▼, significantly associated with lower occurrence of the outcome; ▽, non-significantly associated with lower occurrence of the outcome; ≈, equivalent occurrence of outcome in those with and without the biomarker (utilized e.g., when OR = 1.0).

TABLE 5 Overview: Studies evaluating biomarkers predictive of cutaneous viral infections

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result measures of effect (95% CI)	Result summary	Analysis
FLG and other skin barrier genetic variants						
Gao 2009[36]	Case control (cross-sectional) study, multicenter (setting unclear)	R501X	Eczema herpeticum (at least one episode documented by ADVN investigator or diagnosis by another physician confirmed by HSV PCR, tissue immune-fluorescence, Tzanck smear, and/or culture)	Significant: OR 3.4 (1.7–6.8)	▲	Crude
		2282del4		NS: OR 1.3 (0.7–2.5)	△	
		Both R501X and 2282del4		Significant: OR 2.2 (1.3–3.8)	▲	
		Other FLG polymorphisms		Significant: rs1933063 OR 0.24 (0.07–0.82)	▼	
				NS: rs2065956 OR 0.98 (0.51–1.88)	▽	
				NS: rs12730241 OR 1.73 (0.99–3.02)	△	
				NS: rs11582620 OR 1.34 (0.74–2.44)	△	
			Assessed at mean age 32.6 (±17.6) years	NS: rs1933064 OR 1.16 (0.52–2.58)	△	
				NR: rs3126082, rs6587665, rs11204980, rs3126091 sequenced but not present in the European American cohort)	NR	
n = 273 (European American adults/children)						
n = 186 (African American adults/children)		R501X		Significant: OR 5.28 (1.0–27.4) *p*-value = 0.0289	▲	
		2282del4		NS: OR 0.35 (0.01–16.6)	▽	
		Other FLG polymorphisms		Significant: rs2065956 OR 4.11 (1.34–12.59)	▲	
				NS: rs12730241 OR 2.64 (0.93–7.49)	△	
				NS: rs11582620 OR 1.90 (0.36–9.93)	△	
				NS: rs3126082 OR 0.69 (0.23–2.08)	▽	
				NS: rs6587665 OR 0.65 (0.14–3.11	▽	
				NS: rs11204980 OR 1.92 (0.60–6.21)	△	
				NS: rs1933064 OR 1.46 (0.16–13.70)	△	
				NS: rs3126091 OR 0.87 (0.29–2.61)	▽	
				NS: rs1933063 OR not reported, *p*-value = 0.6565	NR	
Luukkonen 2017[53]	Prospective cohort, single center (skin and allergy hospital)	R501X	History of HSV symptoms (NR)	NS: OR 3.80 (0.89–16.16)	△	Crude
n = 424 (adults/children)		2282del4	Mean age inclusion for assessment 32.3 (±14.9) years, 1 year f/u	NS: OR 0.69 (0.30–1.66)	▽	
		R2447X		NS: OR 0.51 (0.11–2.38)	▽	
		R501X, 2282del14, or R2447X		NS: OR 0.84 (0.43–1.66)	▽	
TSLP genetic variants						
Gao 2010[37]	Case–control (cross-sectional) study, multicenter (setting unclear)	TSLP SNPs - rs2289276, rs1898671, rs11466749, rs2416259,	Eczema herpeticum (at least one episode documented by ADVN investigator or diagnosis by another physician confirmed by HSV PCR, tissue immune-fluorescence, Tzanck smear, and/or culture)	NS: rs2289276 OR 1.2 (0.7–2.1)	△	Crude
n = 273 (European American adults/children)				Significant: rs1898671 OR 0.6 (0.4–0.9)	▼	
				NS: rs11466749 OR 0.7 (0.3–1.3)	▽	
				Significant: rs2416259 OR 2.0 (1.1–3.6)	▲	
		TSLP SNPs - rs991035, rs764916, rs10043985, rs1837253, rs17551370, rs3806933, rs10062929, rs2289277, rs10035870, rs11466749, rs11466750		ORs and CIs, nor *p*-values reported	NR	
			Assessed at mean age 32.6 (±17.6) years			
		TSLPR SNPs - rs36139698, rs36177645, rs36133495		NS: rs36139698 OR 0.9 (0.5–1.5)	▽	
				NS: rs36177645 OR 1.6 (0.9–2.7)	△	
				NS: rs36133495 OR 1.2 (0.6–2.5)	△	
		TSLP:TSLPR gene interaction (TSLP rs1898671 and TSLPR rs36139698)		Significant: OR for interaction (TSLP rs1898671 and TSLPR rs36139698) 2.32 *p*-value = 0.011	▲	
		TSLP:IL7R gene interactions (TSLP rs10062929 and IL7R rs11957503, TSLP rs11466749 and IL7R rs11957503)		Significant: OR for interaction (TSLP rs10062929 and IL7R rs11957503) 4.59, *p*-value = 0.014	▲	
				Significant: OR for interaction (TSLP rs11466749 and IL7R rs11957503) 3.06, *p*-value = 0.020	▲	

TABLE 5 (Continued)

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result measures of effect (95% CI)	Result summary	Analysis
Interferon-related genetic variants						
Gao 2012[35] *n* = 278 (European American adults/ children)	Case–control (cross-sectional) study, multicenter (setting unclear)	IRF2 SNPs - rs7667268, rs807684, rs17488073, rs809909, rs11132242, rs3775543, rs1342852, rs1124191	Eczema herpeticum (at least one episode documented by ADVN investigator or diagnosis by another physician confirmed by HSV PCR, tissue immune-fluorescence, Tzanck smear, and/or culture) Assessed at mean age 32.6 (±17.6) years	NS: rs807684 OR 1.87 (0.99–3.51), Cochran-Armitage *p*-value corrected for multiple testing (adjusted Cochran-Armitage *p*-value) = 0.083	△	Crude OR and 95% CI. *p*-values based on Cochran-Armitage trend test are adjusted for multiple testing
				Significant: rs17488073 OR 0.52 (0.27–0.95), adjusted Cochran-Armitage *p*-value = 0.034	▼	
				Significant: rs809909 OR 0.59 (0.38–0.90), adjusted Cochran-Armitage *p*-value = 0.022	▼	
				Significant (based on adjusted Cochran-Armitage *p*-value): rs11132242 OR 1.60 (0.99–2.60), Cochran-Armitage *p*-value = 0.009, adjusted Cochran-Armitage *p*-value = 0.049	△unadjusted OR ▲ corrected for multiple testing	
				Significant (based on unadjusted OR): rs3775543 OR 2.50 (1.02–6.11), Cochran-Armitage *p*-value = 0.023 adjusted Cochran-Armitage *p*-value = 0.061	▲unadjusted OR △ corrected for multiple testing	
				Significant: rs1342852 OR 1.62 (1.07–2.44), adjusted Cochran-Armitage *p*-value = 0.043	▲	
				Significant: rs1124191 OR 0.49 (0.27–0.88), adjusted Cochran-Armitage *p*-value = 0.022	▼	
				Unclear: rs7667268 (possible error/discrepancy in the manuscript). Minor allele frequency (MAF) amongst cases of eczema herpeticum = 0.75 and MAF amongst controls = 0.17, implying minor allele is associated with eczema herpeticum, however OR for the minor allele is reported as 0.39 (0.13–1.03, adjusted Cochran-Armitage *p*-value = 0.104	unclear	
		IRF2 5-SNP haplotypes - rs3775552 (C/A)/ rs809909 (A/T)/ rs7655371 (G/A)/ rs6812958 (G/A)/ rs2797507(C/A)		NS: CTGAA haplotype, *p*-value = 0.5099	△	
				Significant: CAGGA haplotype, *p*-value = 0.0008	▼	
				Significant: CTAGC haplotype, *p*-value = 0.0397	▲	
				NS: AAGGC haplotype, *p*-value = 0.0967	▽	
				NS: CAGGC haplotype, *p*-value = 0.1503	△	
				NS: CTGGC haplotype, *p*-value = 0.4230	△	

(Continues)

TABLE 5 (Continued)

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result measures of effect (95% CI)	Result summary	Analysis
Gao 2015[34] *n* = 228 (European American adults/ children)	Case–control (cross-sectional) study, multicenter (setting unclear)	7 individual IFNGR1 SNPs - rs11914, rs17175127, rs1327475, rs10457655, rs7749390, rs2234711, rs28515059	Eczema herpeticum (at least one episode documented by ADVN investigator or diagnosis by another physician confirmed by HSV PCR, tissue immune-fluorescence, Tzanck smear, and/or culture) Assessed at mean age 29.9 (±NR) years	Significant: rs11914 OR 0.42 (0.24–0.72)	▼	Crude
				Significant: rs17175127 OR 0.42 (0.24–0.7)	▼	
				Significant: rs1327475 OR 0.43 (0.25–0.73) (previously reported using the same cohort in Leung 2011,[50] *n* = 278)	▼	
				Significant: rs10457655 OR 0.42 (0.24–0.72)	▼	
				Significant: rs7749390 OR 0.66 (0.48–0.91) (previously reported using the same cohort in Leung 2011,[50] *n* = 278)	▼	
				Significant: rs2234711 OR 0.67 (0.49–0.92)	▼	
				Significant: rs28515059 OR 0.46 (0.30–0.71)	▼	
		IFNGR1 2-SNP haplotype - rs10457655/rs7749390 (AG)		Significant: AG haplotype OR 0.41 (0.25–0.66) (as reported using the same cohort in Leung 2011,[50] *n* = 278)	▼	
		IFNGR1 3- to 7- SNP haplotypes		Significant: AGG haplotype OR 0.43 (0.27–0.69)	▼	
				Significant: AAGG haplotype OR 0.44 (0.27–0.72)	▼	
				Significant: AAAGG haplotype OR 0.44 (0.27–0.71)	▼	
				Significant: AAAGGA haplotype OR 0.44 (0.27–0.72)	▼	
				Significant: CAAAGGA haplotype OR 0.44 (0.27–0.72)	▼	
		IFNAR1 variants		NS: OR and CI not reported	NR	
Leung 2011[50] *n* = 278 (European American adults/children)	Case–control (cross-sectional) study, multicenter (setting unclear)	IFNGR1 SNPs - rs7749390, rs1327475, rs1045655	Eczema herpeticum (at least one episode documented by ADVN investigator or diagnosis by another physician confirmed by HSV PCR, tissue immune-fluorescence, Tzanck smear, and/or culture) Assessed at mean age 32.6 (±17.6) years	Significant (based on adjusted Cochran-Armitage *p*-value): rs7749390 OR 0.67 (0.41–1.10), Cochran-Armitage *p*-value = 0.033	▽unadjusted OR ▼ Cochran-Armitage *p*-value direction of effect not reported	Crude
				Significant: rs1327475 OR (NR), Cochran-Armitage *p*-value = 0.012		
				Significant: rs1045655 OR (NR), Cochran-Armitage *p*-value = 0.001		
		IFNGR1 2-SNP haplotypes - rs10457655 (A/G)/rs7749390 (A/G)		Significant: AG haplotype OR 0.46 (0.24–0.87)	▼	
		IFNG SNPs - rs2069727, rs2069718, rs2069716, rs2430561		NS: neither *p*-values nor OR reported	NR	
		IFNG 4-SNP haplotypes - rs2069727 (C/T)/rs2069718 (G/A)/rs2069716 (C/T)/rs2430561 (A/T)		NS: CGCA haplotype OR 1.2 (0.42–3.93), Cochran-Armitage *p*-value = 0.60	△	
				NS: CGTA haplotype OR 0.84 (0.51–1.38), Cochran-Armitage *p*-value = 0.337	▽	
				Significant (based on Cochran-Armitage trend test): TGTA haplotype, OR 4.64 (0.92–23.4) (Cochran-Armitage *p*-value = 0.0027)	△unadjusted OR ▲Cochran-Armitage *p*-value	
				NS: TATT haplotype OR 1.08 (0.66–1.77), Cochran-Armitage *p*-value = 0.664	△	
				NS: TGTT haplotype OR 0.74 (0.36–1.52), Cochran-Armitage *p*-value = 0.332	▽	

TABLE 5 (Continued)

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result measures of effect (95% CI)	Result summary	Analysis
Other genetic variants						
Gao 2010[37] *n* = 273 (European American adults/children)	Case–control (cross-sectional) study, multicenter (setting unclear)	IL7R SNPs - rs12516866, rs10213865, rs1389832, rs1053496, rs10058453	Eczema herpeticum (at least one episode documented by ADVN investigator or diagnosis by another physician confirmed by HSV PCR, tissue immune-fluorescence, Tzanck smear, and/or culture) Assessed at mean age 32.6 (±17.6) years	Significant: rs12516866 OR 0.6 (0.3–1.0), *p*-value = 0.044 Significant: rs10213865 OR 0.6 (0.3–1.0), *p*-value = 0.027 Significant: rs1389832OR 2.0 (1.1–3.7) NS: rs1053496 OR 1.2 (0.7–2.1) Significant: rs10058453 OR 1.9 (1.1–3.4)	▼ ▼ ▲ △ ▲	Crude
		IL7R SNPs - rs1353251, rs11567714, rs7737000, rs11567762, rs10063294, rs11957503		OR and CI, nor *p*-value reported	NR	
Howell 2011[46] *n* = 278 (European American adults/children)	Case–control (cross-sectional) study, multicenter (setting unclear)	STAT6 SNPs - rs12368672, rs324013, rs167769, rs324011, rs841718, rs3024975, rs324015, rs703817	Eczema herpeticum (at least one episode documented by ADVN investigator or diagnosis by another physician confirmed by HSV PCR, tissue immune-fluorescence, Tzanck smear, and/or culture) Assessed at mean age 32.6 (±17.6) years	NS: rs12368672 OR 0.78 (0.49–1.24), Cochran-Armitage *p*-value = 0.276 NS: rs324013 OR 0.82 (0.56–1.19), Cochran-Armitage *p*-value = 0.285 Significant: rs167769 OR 0.65 (0.43–0.98), Cochran-Armitage *p*-value = 0.027 NS: rs324011 OR 0.70 (0.47–1.01), Cochran-Armitage *p*-value = 0.060 Significant: rs841718 OR 1.66 (1.14–2.41), Cochran-Armitage *p*-value) = 0.006 Significant: rs3024975 OR 2.14 (1.15–4.02), Cochran-Armitage *p*-value = 0.009 NS: rs324015 OR 1.05 (0.68–1.62), Cochran-Armitage *p*-value = 0.818 Significant (based on Cochran-Armitage trend test): rs703817 OR 1.40 (0.92–2.15), Cochran-Armitage *p*-value = 0.029	▽ ▽ ▼ ▽ ▲ ▲ △ △unadjusted OR ▲ Cochran-Armitage trend test	Crude
		STAT6 2-SNP haplotypes - rs167769 (C/T) / rs324013 (C/T)		NS: CC haplotype OR 0.77 (0.43–1.40), Cochran-Armitage *p*-value = 0.210 Significant: CT haplotype OR 3.33 (1.39–8.55), Cochran-Armitage *p*-value = 5.17×10^{-6} Significant (based on Cochran-Armitage trend test): TT haplotype OR 0.66 (0.31–1.24), Cochran-Armitage *p*-value = 0.038	▽ ▲ ▽unadjusted OR ▼Cochran-Armitage trend test	

(Continues)

TABLE 5 (Continued)

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result measures of effect (95% CI)	Result summary	Analysis
Mathias 2013[60] *n* = 286 (European American children/adults)	Case control (cross-sectional) study, multicenter (setting unclear)	MHC class I alleles	Eczema herpeticum (at least one episode documented by ADVN investigator or diagnosis by another physician confirmed by HSV PCR, tissue immune-fluorescence, Tzanck smear, and/or culture) Assessed at mean age 29.9 (range: 1.3–80.7) years	NS: A*01 OR 1.23 (0.74–2.03) NS: A*02 OR 0.86 (0.54–1.37) NS: A*03 OR 1.09 (0.62–1.90) NS: A*11 OR 0.84 (0.41–1.73) NS: A*24 OR 1.60 (0.82–3.10) Significant: B*07 OR 1.91 (1.1–3.31) Significant: B*07:ANVB OR 1.98 (1.12–3.50) NS: B*08 OR 0.69 (0.39–1.20) NS: B*18 OR 1.22 (0.55–2.70) NS: B*27 OR 1.33 (0.64–2.78) NS: B*35 OR 0.82 (0.41–1.64) NS: B*44 OR 0.67 (0.40–1.12) NS: B*51 OR 1.42 (0.70–2.89) NS: B*62 OR 1.89 (0.97–3.66) NS: C*04 OR 0.88 (0.48–1.63) NS: C*05 OR 0.75 (0.41–1.38) NS: C*06 OR 1.00 (0.48–2.10) NS: C*07 OR 0.93 (0.58–1.48) NS: C*10 OR 1.35 (0.70–2.59) NS: C*12 OR 1.24 (0.60–2.57)	△ ▽ △ ▽ △ ▲ ▲ ▽ △ △ ▽ ▽ △ △ ▽ ▽ ≈ ▽ △ △	Crude
Gao 2015[34] *n* = 228 (European American adults/children)	Case control (cross-sectional) study, multicenter (setting unclear)	IL12RB1 variants	Eczema herpeticum (at least one episode documented by ADVN investigator or diagnosis by another physician confirmed by HSV PCR, tissue immune-fluorescence, Tzanck smear, and/or culture) Assessed at mean age 29.9 (±NR) years	NS: OR and CI not reported	NR	Crude

Note: Ages at which genetic biomarkers measured not relevant, so not included in table.

Abbreviations: CI, confidence interval; HSV, herpes simplex virus; IFNAR1, interferon-alpha receptor 1; IFNGR1, interferon-gamma receptor 1; IL12RB1, IL-12 receptor, beta 1; IL7R, interleukin 7 receptor; IRF2, interferon regulatory factor 2; MHC, major histocompatibility complex; NR, not reported; NS, not significant; OR, odds ratio; PCR, polymerase chain reaction; SNP, single nucleotide polymorphism; STAT6, signal transducer and activator of transcription 6; TSLP, thymic stromal lymphopoietin; TSLPR, TSLP receptor; ▲, presence of the biomarker is significantly associated with higher occurrence of the outcome; △, non-significantly associated with higher occurrence of the outcome; ▼, significantly associated with lower occurrence of the outcome; ▽, non-significantly associated with lower occurrence of the outcome; ≈, equivalent occurrence of outcome in those with and without the biomarker (utilized e.g. when OR = 1.0).

TABLE 6 Overview: Studies evaluating biomarkers predictive of other comorbidities, including ichthyosis, neuropsychiatric disorders and malignancies

Study participants analyzed	Design and setting	Biomarker Age measured	Outcome (assessment method) Age assessed	Result measures of effect (95% CI)	Result summary	Analysis
FLG and other skin barrier genetic variants						
Ezzedine 2012[32] *n* = 110 (adults)	Cross-sectional study, single center (dermatology department)	R501X	Ichthyosis vulgaris (clinical judgement by senior dermatologist) Assessed at mean age 36 (±16.2) years	NS: OR 1.33 (0.40–4.40)	△	Crude
		2282del4		Significant: OR 5.41 (1.92–15.21)	▲	
		R501X or 2282del4		Significant: OR 4.69 (1.93–11.38)	▲	
Heede 2017[42] *n* = 223 (adults)	Cross-sectional study, single center (dermatology department)	R501X, 2282del14, or R2447X	Actinic keratosis (self-reported lifetime prevalence of doctor's diagnosis) Assessed at median age of 42 years	Significant: OR 4.02 (1.23–13.2)	▲	Crude
n = 224 (adults)			Anxiety (self-reported lifetime prevalence of doctor's diagnosis) Assessed at median age of 42 years	NS: OR 1.05 (0.32–3.47)	△	
n = 226 (adults)			Depression (self-reported lifetime prevalence of doctor's diagnosis) Assessed at median age of 42 years	NS: OR 1.12 (0.53–2.36)	△	
n = 231 (adults)			Melanoma (self-reported lifetime prevalence of doctor's diagnosis) Assessed at median age of 42 years	NS: OR 2.75 (0.17–44.72)	△	
			Non-melanoma skin cancer (self-reported lifetime prevalence of doctor's diagnosis) Assessed at median age of 42 years	NS: OR 5.60 (0.50–62.9)	△	

Note: Ages at which genetic biomarkers measured not relevant, so not included in table.

Abbreviations: CI, confidence interval; FLG, filaggrin; NS, not significant; OR, odds ratio; ▲, presence of the biomarker is significantly associated with higher occurrence of the outcome; △, non-significantly associated with higher occurrence of the outcome; ▼, significantly associated with lower occurrence of the outcome; ▽, non-significantly associated with lower occurrence of the outcome; ≈, equivalent occurrence of outcome in those with and without the biomarker (utilized e.g. when OR = 1.0).

a significant association with actinic keratosis, but not with melanoma, non-melanoma skin cancer, anxiety, or depression (Table 6).[42]

4 | DISCUSSION

4.1 | Summary of findings

We performed a systematic review and critical appraisal of the literature relevant to biomarkers which predict the development of comorbidities in patients with AD. The majority of the identified studies investigated the association between candidate biomarkers and the development of allergic diseases which characterize the atopic march, as well as with hand eczema, ACD, and the severe viral infection, EH. Some of the results are promising, particularly with regards to asthma, where s-IgE and/or SPTs may play a role in predicting which patients are at risk for developing asthma or wheezing phenotype. Biomarkers predicting the development of asthma and food allergies would be extremely useful; early intervention in targeted populations could prevent the associated morbidity and mortality. Associations between EH and various genetic variants, including FLG mutations, TSLP mutations, and interferon-related

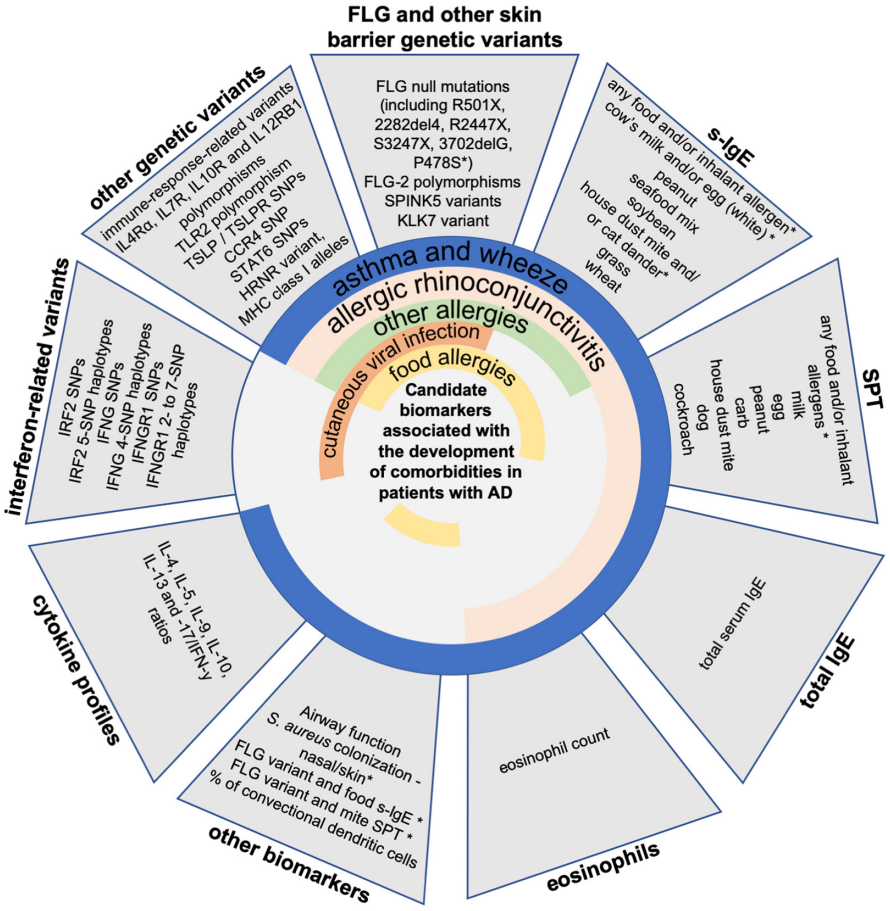

FIGURE 2 Graphical representation of candidate biomarkers associated with comorbidities in patients with atopic dermatitis. The inner ring chart lists the comorbidities evaluated in this systematic review, and the outer spokes categorize the biomarkers by function. The overlap between spokes and inner rings identifies which biomarker types were evaluated for which comorbidity. AD, atopic dermatitis; CCR4, C-C chemokine receptor type 4; FLG, filaggrin; HRNR, hornerin; IFNG, interferon gamma; IFNGR1, interferon-gamma receptor 1; IgE, immunoglobulin E; IL, interleukin; IL4Rα, IL-4 receptor alpha; IL5RA, IL-5 receptor alpha; IL7R, IL-7 receptor; IL10R, IL-10 receptor; IL12RB1, IL-12 receptor, beta 1; IRF2, interferon regulatory factor 2; KDR, kinase insert domain receptor; KLK7, kallikrein related peptidase 7; MHC, major histocompatibility complex; s-IgE, specific IgE; SNP, single nucleotide polymorphism; SPINK5, serine peptidase inhibitor Kazal type 5; SPT, skin prick test; STAT6, signal transducer and activator of transcription 6; TLR2, toll-like receptors; TSLP, thymic stromal lymphopoietin; TSLPR, TSLP receptor. *Candidate biomarkers were assessed individually and composite

variants, also appear to be promising. Although, EH is less frequently observed in AD patients compared with asthma (7%–10%), validated biomarkers to identify those at highest risk would be clinically useful, as targeted preventative strategies could reduce serious and/or vision-threatening complications of EH.[83]

Filaggrin LOF mutations were frequently investigated as candidate biomarkers, and while they are highly relevant to the aetiopathogenesis of AD, LOF mutations are neither essential, nor sufficient to predict the development of AD.[84] From our results, the role of FLG LOF mutations in stratifying patients with AD according to their risk of comorbidity development also appears to be limited. It was intriguing to note that the combination of skin barrier defects (FLG LOF mutations) and aberrant immunological phenotype (elevated s-IgE to food/environmental allergens) demonstrated statistically significant associations with asthma/wheezing in 3 of 4 early life cohorts (LISA, MAS, and Childhood Environment and Allergic Diseases Cohort, but not significant in GINI).[33,55,76] This reinforces the importance of further research to clarify how skin barrier defects interact with environmental triggers to initiate and perpetuate Th2-driven inflammation in AD and associated atopic diseases.

4.2 | Strength and limitations of our systematic review

This review is the first systematic review of all published studies evaluating biomarkers which predict the development of comorbidities in patients with AD. The review provides a comprehensive and recently updated search (September 2021) of multiple databases. Quality and risk of bias assessments were conducted using Cochrane's recommended QUIPS tool. This systematic review was conducted by members of BIOMAP including clinicians, patient representatives, and academic and industry researchers, and thus

interpretation of the included studies' findings was considered from the clinical, as well as the methodological perspective.

The quality of included studies varied, and QUIPS assessment revealed moderate-to-high risk of bias in the majority of studies, particularly with regards to the study participation and study confounding domains. Some studies measured candidate biomarkers only in a subgroup, and the number of subjects included in the analysis relevant for this review was not always apparent, which may indicate selection bias. Moreover, for the majority of included studies, details about the recruitment processes and participants characteristic were poorly reported. Included studies also frequently suffered from loss-to-follow-up or from insufficient reporting of follow-up. A major limitation of the available biomarker research is a lack of adjustment in the majority of included studies. Where there was adjustment for confounding, this was often incomplete, and in particular, there was limited adjustment for AD severity.

Ultimately, heterogeneity of study design, biomarker measurement, and cut-off thresholds, follow-up periods and outcome assessment has limited the clinical utility of current biomarker research in AD, and prevented pooling of data, or meta-analysis of results, in this systematic review.

4.3 | Suggestions for future research

Differences in ethnic groups within and between the studies, lack of adequate reporting of ethnicity, or the small number of studies of individual ethnic groups (i.e., five studies in an Asian population[48,74,76,77,82]) must also be considered critically. There is evidence for differences in the epidemiology, phenotype, genetics, and associated comorbidities of AD amongst different ethnic subgroups.[85,86] In addition, prior studies found marked racial- and ethnicity-specific differences in biomarkers, for example, cardiovascular biomarkers, biomarkers for pediatric reference intervals, and biomarkers use in cancer diagnosis and treatment.[87–89] Within this review, results published by Gao et al.[36] demonstrated conflicting associations between the FLG variants (rs1933063 and rs2065956) and risk of EH in European Americans compared with African Americans. Thus, the utility of any proposed candidate biomarkers will need to be evaluated across and between different ethnic groups.

All studies assessing specific genetic variants have used the wild-type or the presence of minor (risk) allele as the reference comparison. In contrast, a number of different positive cut-off values were used for SPTs, total serum IgE, and s-IgE (e.g., RAST class > 1 and RAST class > 2). The adoption of standardized cut-offs would improve the comparability of studies, and the importance of this was previously discussed in a similar context.[90]

Non-invasive biomarkers which can be serially measured in children from birth (for example, tape strips, microbiome studies using skin swabs) is a relatively unexplored area of research which warrants further investigation. We did not identify any studies which evaluated gene transcription, or epigenetic modulation, which are increasingly used to study disease trajectory, comorbidity development, and response to treatment. Research evaluating biomarkers associated with autoimmune, gastrointestinal, malignant, and cardiovascular diseases in AD patients is currently poorly developed. Despite an increasing body of evidence linking AD with neuropsychiatric comorbidities[91] including depression,[92–94] anxiety,[93] and ADHD,[95] we identified only a single study which assessed candidate biomarkers.[42] Predicting who is at risk of developing neurocognitive and psychiatric comorbidities may encourage a more holistic approach to assessing and treating people with AD, and further research in this field would be valuable.

BIOMAP brings together existing data from over 60 individual cohorts (including many cohorts included within this review), and harmonization of clinical and molecular datasets is underway which will allow for replication and validation of existing analyses and novel cross-cohort comparisons.[96] In prospectively designed research, standardization of these aspects may also allow for more definitive conclusions to be drawn. Further research should aim to adjust for confounding variables, including family history of atopy and AD severity, using standardized assessment tools.

5 | CONCLUSION

In conclusion, the ability to predict the development of comorbidities remains a key unmet need in patients for AD. While several of the studies included in this review presented promising results, further evaluation is required before they can be advanced into routine clinical use.

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CONFLICT OF INTEREST

CB, SZ, KVB and BA have no conflicts of interest to declare relating to this work. KE has received grants and personal fees from AbbVie, Almirall, BMS, Lilly, Leo, Janssen, Novartis, UCB, and Sanofi. SW has received institutional research grants from Sanofi Deutschland GmbH, LEO Pharma, and La Roche Posay, has performed consultancies for Abbvie, Eli Lilly, Galderma, Kymab, LEO

Pharma, Pfizer, Novartis, Sanofi-Genzyme, and Regeneron, he has also lectured at educational events sponsored by Abbvie, Eli Lilly, LEO Pharma, Sanofi-Genzyme, and Regeneron, and is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of psoriasis and atopic dermatitis. JR is an employee of UCB and holds shares in UCB. AZ has been an advisor and/or received speaker's honoraria and/or received grants and/or participated in clinical trials of the following companies: AbbVie, Almirall, Amgen, Beiersdorf Dermo Medical, Bencard Allergie, BMS, Celgene, Eli Lilly, GSK, Janssen Cilag, Leo Pharma, Miltenyi Biotec, Novartis, Pfizer, Sanofi-Aventis, Takeda Pharma, UCB Pharma. CF is chief investigator of the UK National Institute for Health Research–funded TREAT (ISRCTN15837754) and SOFTER (ClinicalTrials.gov: NCT03270566) trials and the UK-Irish Atopic Eczema Systemic Therapy Register (A-STAR; ISRCTN11210918) and is a principal investigator in the European Union Horizon 2020–funded BIOMAP Consortium (http://www.biomap-imi.eu/). He is also the CI of the EU Joint Programme Initiative-funded TRANS-FOODS consortium. His department has also received funding from Sanofi-Genzyme.

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REFERENCES

1. 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(6):1526-1532.
2. Abuabara K, Yu AM, Okhovat JP, Allen IE, Langan SM. The prevalence of atopic dermatitis beyond childhood: a systematic review and meta-analysis of longitudinal studies. *Allergy*. 2018;73(3):696-704.
3. Bylund S, Kobyletzki LB, Svalstedt M, Svensson A. Prevalence and incidence of atopic dermatitis: a systematic review. *Acta Derm Venereol*. 2020;100(12):320-329.
4. Laughter MR, Maymone MBC, Mashayekhi S, et al. The global burden of atopic dermatitis: lessons from the global burden of disease study 1990-2017. *Br J Dermatol*. 2021;184(2):304-309.
5. Sacotte R, Silverberg JI. Epidemiology of adult atopic dermatitis. *Clin Dermatol*. 2018;36(5):595-605.
6. 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. *Allergy*. 2020;75(11):2936-2938.
7. Ring J, Zink A, Arents BWM, et al. Atopic eczema: burden of disease and individual suffering - results from a large EU study in adults. *J Eur Acad Dermatol Venereol*. 2019;33(7):1331-1340.
8. Zink AGS, Arents B, Fink-Wagner A, et al. Out-of-pocket costs for individuals with atopic eczema: a cross-sectional study in nine European countries. *Acta Derm Venereol*. 2019;99(3):263-267.
9. Weidinger S, Novak N. Atopic dermatitis. *Lancet*. 2016;387(10023):1109-1122.
10. Brunner PM, Silverberg JI, Guttman-Yassky E, et al. Increasing comorbidities suggest that atopic dermatitis is a systemic disorder. *J Invest Dermatol*. 2017;137(1):18-25.
11. Galli SJ. Toward precision medicine and health: opportunities and challenges in allergic diseases. *J Allergy Clin Immunol*. 2016;137(5):1289-1300.
12. Bieber T, D'Erme AM, Akdis CA, et al. Clinical phenotypes and endophenotypes of atopic dermatitis: where are we, and where should we go? *J Allergy Clin Immunol*. 2017;139(4s):S58-S64.
13. Renert-Yuval Y, Thyssen JP, Bissonnette R, et al. Biomarkers in atopic dermatitis-a review on behalf of the international eczema council. *J Allergy Clin Immunol*. 2021;147(4):1174-1190.
14. Thijs JL, de Bruin-Weller MS, Hijnen D. Current and future biomarkers in atopic dermatitis. *Immunol Allergy Clin North Am*. 2017;37(1):51-61.
15. Guttman-Yassky E, Diaz A, Pavel AB, et al. Use of tape strips to detect immune and barrier abnormalities in the skin of children with early-onset atopic dermatitis. *JAMA Dermatol*. 2019;155(12):1358-1370.
16. Thijs J, Krastev T, Weidinger S, et al. Biomarkers for atopic dermatitis: a systematic review and meta-analysis. *Curr Opin Allergy Clin Immunol*. 2015;15(5):453-460.
17. Glickman JW, Han J, Garcet S, Krueger JG, Pavel AB, Guttman-Yassky E. Improving evaluation of drugs in atopic dermatitis by combining clinical and molecular measures. *J Allergy Clin Immunol Pract*. 2020;8(10):3622-3625.
18. Tham EH, Leung DY. Mechanisms by which atopic dermatitis predisposes to food allergy and the atopic march. *Allergy Asthma Immunol Res*. 2019;11(1):4-15.
19. FDA-NIH Biomarker Working Group. *BEST (Biomarkers, EndpointS, and Other Tools) Resource*. Silver Spring; 2016.
20. Broderick C, Lewis S, VanBart K, et al. A systematic review of biomarkers that predict comorbidity development in atopic dermatitis. PROSPERO; 2020. Accessed December 2022. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=193294
21. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
22. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. *J Clin Epidemiol*. 2016;75:40-46.
23. Morrison A, Polisena J, Husereau D, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. *Int J Technol Assess Health Care*. 2012;28(2):138-144.
24. Review Manager (RevMan) [Computer program]. Version 5.4. Copenhagen 2014; 2020. Accessed December 2022. https://training.cochrane.org/system/files/uploads/protected_file/RevMan5.4_user_guide.pdf
25. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med*. 2006;144(6):427-437.
26. Ballardini N, Bergström A, Böhme M, et al. Infantile eczema: prognosis and risk of asthma and rhinitis in preadolescence. *J Allergy Clin Immunol*. 2014;133(2):594-596.
27. Bonnelykke K, Pipper CB, Tavendale R, Palmer CN, Bisgaard H. Filaggrin gene variants and atopic diseases in early childhood assessed longitudinally from birth. *Pediatr Allergy Immunol*. 2010;21(6):954-961.
28. Chang J, Mitra N, Hoffstad O, Margolis DJ. Association of filaggrin loss of function and thymic stromal lymphopoietin variation with treatment use in pediatric atopic dermatitis. *JAMA Dermatol*. 2017;153(3):275-281.
29. Cosickic A, Skokic F, Selimovic A, et al. Development of respiratory allergies, asthma and allergic Rhinits in children with atopic dermatitis. *Acta Clin Croat*. 2017;56(2):308-317.

30. Debinska A, Danielewicz H, Drabik-Chamerska A, Kalita D, Boznanski A. Filaggrin loss-of-function mutations as a predictor for atopic eczema, allergic sensitization and eczema-associated asthma in polish children population. *Adv Clin Exp Med*. 2017;26(6):991-998.
31. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015;372(9):803-813.
32. Ezzedine K, Droitcourt C, Ged C, et al. Usefulness of a global clinical ichthyosis vulgaris scoring system for predicting common FLG null mutations in an adult caucasian population. *Br J Dermatol*. 2012;167(5):1165-1169.
33. Filipiak-Pittroff B, Schnopp C, Berdel D, et al. Predictive value of food sensitization and filaggrin mutations in children with eczema. *J Allergy Clin Immunol*. 2011;128(6):1235-1241.
34. Gao L, Bin L, Rafaels NM, et al. Targeted deep sequencing identifies rare loss-of-function variants in IFNGR1 for risk of atopic dermatitis complicated by eczema herpeticum. *J Allergy Clin Immunol*. 2015;136(6):1591-1600.
35. Gao PS, Leung DY, Rafaels NM, et al. Genetic variants in interferon regulatory factor 2 (IRF2) are associated with atopic dermatitis and eczema herpeticum. *J Invest Dermatol*. 2012;132(3 Pt 1):650-657.
36. Gao PS, Rafaels NM, Hand T, et al. Filaggrin mutations that confer risk of atopic dermatitis confer greater risk for eczema herpeticum. *J Allergy Clin Immunol*. 2009;124(3):507-513.
37. Gao PS, Rafaels NM, Mu D, et al. Genetic variants in thymic stromal lymphopoietin are associated with atopic dermatitis and eczema herpeticum. *J Allergy Clin Immunol*. 2010;125(6):1403-1407.
38. Greisenegger E, Novak N, Maintz L, et al. Analysis of four prevalent filaggrin mutations (R501X, 2282del4, R2447X and S3247X) in Austrian and German patients with atopic dermatitis. *J Eur Acad Dermatol Venereol*. 2010;24(5):607-610.
39. Greisenegger EK, Zimprich F, Zimprich A, Gleiss A, Kopp T. Association of the chromosome 11q13.5 variant with atopic dermatitis in Austrian patients. *Eur J Dermatol*. 2013;23(2):142-145.
40. Gustafsson D, Sjoberg O, Foucard T. Development of allergies and asthma in infants and young children with atopic dermatitis - a prospective follow-up to 7 years of age. *Allergy*. 2000;55(3):240-245.
41. Heede NG, Thyssen JP, Thuesen BH, Linneberg A, Johansen JD. Anatomical patterns of dermatitis in adult filaggrin mutation carriers. *J Am Acad Dermatol*. 2015;72(3):440-448.
42. Heede NG, Thyssen JP, Thuesen BH, et al. Health-related quality of life in adult dermatitis patients stratified by filaggrin genotype. *Contact Dermatitis*. 2017;76(3):167-177.
43. Henderson J, Northstone K, Lee SP, et al. The burden of disease associated with filaggrin mutations: a population-based, longitudinal birth cohort study. *J Allergy Clin Immunol*. 2008;121(4):872-877.e879.
44. Hertz A, Azulay-Abulafia L, Nascimento APD, Ohara CY, Kuschnir FC, Porto LC. Analysis of filaggrin 2 gene polymorphisms in patients with atopic dermatitis. *An Bras Dermatol*. 2020;95(2):173-179.
45. Holm JG, Thomsen SF. Omalizumab for atopic dermatitis: evidence for and against its use. *G Ital Dermatol Venereol*. 2019;154(4):480-487.
46. Howell MD, Gao P, Kim BE, et al. The signal transducer and activator of transcription 6 gene (STAT6) increases the propensity of patients with atopic dermatitis toward disseminated viral skin infections. *J Allergy Clin Immunol*. 2011;128(5):1006-1014.
47. Kayserova J, Sismova K, Zentsova-Jaresova I, et al. A prospective study in children with a severe form of atopic dermatitis: clinical outcome in relation to cytokine gene polymorphisms. *J Investig Allergol Clin Immunol*. 2012;22(2):92-101.
48. Lee S, Wang HY, Kim E, et al. Clinical characteristics and genetic variation in atopic dermatitis patients with and without allergic contact dermatitis. *Eur J Dermatol*. 2018;28(5):637-643.
49. Lesiak A, Kuna P, Zakrzewski M, et al. Combined occurrence of filaggrin mutations and IL-10 or IL-13 polymorphisms predisposes to atopic dermatitis. *Exp Dermatol*. 2011;20(6):491-495.
50. Leung DY, Gao PS, Grigoryev DN, et al. Human atopic dermatitis complicated by eczema herpeticum is associated with abnormalities in IFN-γ response. *J Allergy Clin Immunol*. 2011;127(4):965-973.
51. Lodge CJ, Lowe AJ, Gurrin LC, et al. House dust mite sensitization in toddlers predicts current wheeze at age 12 years. *J Allergy Clin Immunol*. 2011;128(4):782-788.e789.
52. Lowe AJ, Hosking CS, Bennett CM, et al. Skin prick test can identify eczematous infants at risk of asthma and allergic rhinitis. *Clin Exp Allergy*. 2007;37(11):1624-1631.
53. Luukkonen TM, Kiiski V, Ahola M, et al. The value of FLG null mutations in predicting treatment response in atopic dermatitis: an observational study in Finnish patients. *Acta Derm Venereol*. 2017;97(4):456-463.
54. Marenholz I, Bauerfeind A, Esparza-Gordillo J, et al. The eczema risk variant on chromosome 11q13 (rs7927894) in the population-based ALSPAC cohort: a novel susceptibility factor for asthma and hay fever. *Hum Mol Genet*. 2011;20(12):2443-2449.
55. Marenholz I, Kerscher T, Bauerfeind A, et al. An interaction between filaggrin mutations and early food sensitization improves the prediction of childhood asthma. *J Allergy Clin Immunol*. 2009;123(4):911-916.
56. Marenholz I, Nickel R, Rüschendorf F, et al. Filaggrin loss-of-function mutations predispose to phenotypes involved in the atopic march. *J Allergy Clin Immunol*. 2006;118(4):866-871.
57. Margolis DJ, Gupta J, Apter AJ, et al. Filaggrin-2 variation is associated with more persistent atopic dermatitis in African American subjects. *J Allergy Clin Immunol*. 2014;133(3):784-789.
58. Margolis DJ, Kim B, Apter AJ, et al. Thymic stromal lymphopoietin variation, filaggrin loss of function, and the persistence of atopic dermatitis. *JAMA Dermatol*. 2014;150(3):254-259.
59. Margolis DJ, Mitra N, Wubbenhorst B, et al. Association of filaggrin loss-of-function variants with race in children with atopic dermatitis. *JAMA Dermatol*. 2019;31:31.
60. Mathias RA, Weinberg A, Boguniewicz M, et al. Atopic dermatitis complicated by eczema herpeticum is associated with HLA B7 and reduced interferon-gamma-producing CD8+ T cells. *Br J Dermatol*. 2013;169(3):700-703.
61. Novembre E, Cianferoni A, Lombardi E, Bernardini R, Pucci N, Vierucci A. Natural history of "intrinsic" atopic dermatitis. *Allergy*. 2001;56(5):452-453.
62. Ohshima Y, Yasutomi M, Omata N, et al. Dysregulation of IL-13 production by cord blood CD4+ T cells is associated with the subsequent development of atopic disease in infants. *Pediatr Res*. 2002;51(2):195-200.
63. Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet*. 2006;38(4):441-446.
64. Piancatelli D, Bellotta L, Del Beato T, Duse M, Della Penna MR. Total IL-12 levels are increased in paediatric atopic dermatitis: correlations with age and disease severity. *Int J Immunopathol Pharmacol*. 2008;21(2):359-365.
65. Potaczek DP, Nastalek M, Okumura K, Wojas-Pelc A, Undas A, Nishiyama C. An association of TLR2-16934A >T polymorphism and severity/phenotype of atopic dermatitis. *J Eur Acad Dermatol Venereol*. 2011;25(6):715-721.
66. Ricci G, Patrizi A, Baldi E, Menna G, Tabanelli M, Masi M. Long-term follow-up of atopic dermatitis: retrospective analysis of related risk factors and association with concomitant allergic diseases. *J Am Acad Dermatol*. 2006;55(5):765-771.
67. Ricci G, Patrizi A, Giannetti A, Dondi A, Bendandi B, Masi M. Does improvement management of atopic dermatitis influence the

appearance of respiratory allergic diseases? A follow-up study. *Clin Mol Allergy*. 2010;8:8.
68. Sarria EE, Mattiello R, Yao W, et al. Atopy, cytokine production, and airway reactivity as predictors of pre-school asthma and airway responsiveness. *Pediatr Pulmonol*. 2014;49(2):132-139.
69. Schuttelaar ML, Kerkhof M, Jonkman MF, et al. Filaggrin mutations in the onset of eczema, sensitization, asthma, hay fever and the interaction with cat exposure. *Allergy*. 2009;64(12):1758-1765.
70. Spergel JM, Boguniewicz M, Schneider L, Hanifin JM, Paller AS, Eichenfield LF. Food allergy in infants with atopic dermatitis: limitations of food-specific IgE measurements. *Pediatrics*. 2015;136(6):e1530-e1538.
71. Thyssen JP, Carlsen BC, Menne T, et al. Filaggrin null mutations increase the risk and persistence of hand eczema in subjects with atopic dermatitis: results from a general population study. *Br J Dermatol*. 2010;163(1):115-120.
72. Tran MM, Lefebvre DL, Dharma C, et al. Predicting the atopic march: results from the Canadian healthy infant longitudinal development study. *J Allergy Clin Immunol*. 2018;141(2):601-607 e608.
73. Tsilochristou O, du Toit G, Sayre PH, et al. Association of *Staphylococcus aureus* colonization with food allergy occurs independently of eczema severity. *J Allergy Clin Immunol*. 2019;144(2):494-503.
74. Tsunemi Y, Sekiya T, Saeki H, et al. Lack of association of CCR4 single nucleotide polymorphism with atopic dermatitis in Japanese patients. *Acta Derm Venereol*. 2004;84(3):187-190.
75. Wahn U. Allergic factors associated with the development of asthma and the influence of cetirizine in a double-blind, randomised, placebo-controlled trial: first results of ETAC. Early Treatment of the Atopic Child. *Pediatr Allergy Immunol*. 1998;9(3):116-124.
76. Wang IJ, Lin TJ. FLG P478S polymorphisms and environmental risk factors for the atopic march in Taiwanese children: a prospective cohort study. *Ann Allergy Asthma Immunol*. 2015;114(1):52-57.
77. Wang IJ, Lin TJ, Kuo CF, Lin SL, Lee YL, Chen PC. Filaggrin polymorphism P478S, IgE level, and atopic phenotypes. *Br J Dermatol*. 2011;164(4):791-796.
78. Warner JO. A double-blinded, randomized, placebo-controlled trial of cetirizine in preventing the onset of asthma in children with atopic dermatitis: 18 months' treatment and 18 months' posttreatment follow-up. *J Allergy Clin Immunol*. 2001;108(6):929-937.
79. Weidinger S, O'Sullivan M, Illig T, et al. Filaggrin mutations, atopic eczema, hay fever, and asthma in children. *J Allergy Clin Immunol*. 2008;121(5):1203-1209.e1201.
80. Yao W, Barbe-Tuana FM, Llapur CJ, et al. Evaluation of airway reactivity and immune characteristics as risk factors for wheezing early in life. *J Allergy Clin Immunol*. 2010;126(3):483-488.e481.
81. Ziyab AH, Karmaus W, Zhang H, et al. Association of filaggrin variants with asthma and rhinitis: is eczema or allergic sensitization status an effect modifier? *Int Arch Allergy Immunol*. 2014;164(4):308-318.
82. Ohshima Y, Yamada A, Hiraoka M, et al. Early sensitization to house dust mite is a major risk factor for subsequent development of bronchial asthma in Japanese infants with atopic dermatitis: results of a 4-year followup study. *Ann Allergy Asthma Immunol*. 2002;89(3):265-270.
83. Traidl S, Roesner L, Zeitvogel J, Werfel T. Eczema herpeticum in atopic dermatitis. *Allergy*. 2021;76(10):3017-3027.
84. Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. *Nat Rev Dis Primers*. 2018;4(1):1.
85. Kaufman BP, Guttman-Yassky E, Alexis AF. Atopic dermatitis in diverse racial and ethnic groups-variations in epidemiology, genetics, clinical presentation and treatment. *Exp Dermatol*. 2018;27(4):340-357.
86. Silverberg JI. Racial and ethnic disparities in atopic dermatitis. *Curr Dermatol Rep*. 2015;4(1):44-48.
87. Tahmasebi H, Asgari S, Hall A, et al. Influence of ethnicity on biochemical markers of health and disease in the CALIPER cohort of healthy children and adolescents. *Clin Chem Lab Med*. 2020;58(4):605-617.
88. Hackler E 3rd, Lew J, Gore MO, et al. Racial differences in cardiovascular biomarkers in the general population. *J Am Heart Assoc*. 2019;8(18):e012729.
89. Manne U, Jadhav T, Putcha BK, et al. Molecular biomarkers of colorectal cancer and cancer disparities: current status and perspective. *Curr Colorectal Cancer Rep*. 2016;12(6):332-344.
90. Schoos AM, Hansen SM, Skov FR, et al. Allergen specificity in specific IgE cutoff. *JAMA Pediatr*. 2020;174(10):993-995.
91. Xie QW, Dai X, Tang X, Chan CHY, Chan CLW. Risk of mental disorders in children and adolescents with atopic dermatitis: a systematic review and meta-analysis. *Front Psychol*. 2019;10:1773.
92. Kern C, Wan J, LeWinn KZ, et al. Association of atopic dermatitis and mental health outcomes across childhood: a longitudinal cohort study. *JAMA Dermatol*. 2021;157(10):1200-1208.
93. Schonmann Y, Mansfield KE, Hayes JF, et al. Atopic eczema in adulthood and risk of depression and anxiety: a population-based cohort study. *J Allergy Clin Immunol Pract*. 2020;8(1):248-257.
94. Chatrath S, Lei D, Yousaf M, Chavda R, Gabriel S, Silverberg JI. Longitudinal course and predictors of depressive symptoms in atopic dermatitis. *J Am Acad Dermatol*. 2022;87(3):582-591.
95. Strom MA, Fishbein AB, Paller AS, Silverberg JI. Association between atopic dermatitis and attention deficit hyperactivity disorder in U.S. children and adults. *Br J Dermatol*. 2016;175(5):920-929.
96. Broderick C, Christian N, Apfelbacher C, et al. The BIOMarkers in atopic dermatitis and psoriasis (BIOMAP) glossary: developing a lingua franca to facilitate data harmonization and cross-cohort analyses. *Br J Dermatol*. 2021;185:1066-1069.

SUPPORTING INFORMATION

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

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