


SYSTEMATIC REVIEW

Classifying atopic dermatitis: a systematic review of phenotypes and associated characteristics

A.L. Bosma,^{1,*}  A. Ascott,^{2,†} R. Iskandar,^{3,†} K. Farquhar,⁴ J. Matthewman,⁵ M.W. Langendam,⁶ A. Mulick,³ K. Abuabara,⁷ H.C. Williams,⁸ P.I. Spuls,¹ S.M. Langan,³ M.A. Middelkamp-Hup¹

¹Department of Dermatology, Amsterdam Public Health, Infection and Immunity, Amsterdam UMC, location Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

²Department of Dermatology, Worthing, University Hospitals Sussex NHS Foundation Trust, Worthing, UK

³Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK

⁴NHS Greater Glasgow and Clyde, Glasgow, UK

⁵Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

⁶Department of Epidemiology and Data Science, Amsterdam Public Health Research Institute, Amsterdam UMC, location Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

⁷Department of Dermatology, University of California San Francisco, San Francisco, CA, USA

⁸Centre of Evidence-Based Dermatology, University of Nottingham, Nottingham, UK

*Correspondence: A.L. Bosma. E-mail: a.l.bosma@amsterdamumc.nl

Abstract

Atopic dermatitis is a heterogeneous disease, accompanied by a wide variation in disease presentation and the potential to identify many phenotypes that may be relevant for prognosis and treatment. We aimed to systematically review previously reported phenotypes of atopic dermatitis and any characteristics associated with them. Ovid EMBASE, Ovid MEDLINE and Web of Science were searched from inception till 12 February 2021 for studies attempting to classify atopic dermatitis. Primary outcomes are atopic dermatitis phenotypes and characteristics associated with them in subsequent analyses. A secondary outcome is the methodological approach used to derive them. In total, 8511 records were found. By focussing only on certain clinical phenotypes, 186 studies were eligible for inclusion. The majority of studies were hospital-based (59%, 109/186) and cross-sectional (76%, 141/186). The number of included patients ranged from seven to 526 808. Data-driven approaches to identify phenotypes were only used in a minority of studies (7%, 13/186). Ninety-one studies (49%) investigated a phenotype based on disease severity. A phenotype based on disease trajectory, morphology and eczema herpeticum was investigated in 56 (30%), 22 (12%) and 11 (6%) studies respectively. Thirty-six studies (19%) investigated morphological characteristics in other phenotypes. Investigated associated characteristics differed between studies. In conclusion, we present an overview of phenotype definitions used in literature for severity, trajectory, morphology and eczema herpeticum, including associated characteristics. There is a lack of uniform and consistent use of atopic dermatitis phenotypes across studies.

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Conflicts of interest

ALB, PIS, SML and MAMH are investigators on the European Union Horizon 2020-funded BIOMAP Consortium (<http://www.biomap-imi.eu>). KA received grants for investigator-initiated research to her institution from NIH, National Eczema Foundation, LEO Foundation, Pfizer and Cosmetique International and consulting fees from TARGET RWE. PIS has done consultancies in the past for Sanofi 111017 and AbbVie 041217 (unpaid), receives departmental independent research grants for TREAT NL registry, for which she is Chief Investigator (CI), from different pharma companies since December 2019, is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment, e.g. psoriasis and atopic dermatitis, for which financial compensation is paid to the department/hospital. SML received grants from Wellcome Trust and the Innovative Medicine Initiative Horizon 2020 (BIOMAP project) paid to her institution. AM received a grant from Wellcome Trust paid to her institution. No other disclosures were reported.

[†]Both authors contributed equally and share second authorship Systematic review registration number: CRD42018087500

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Introduction

Atopic dermatitis (AD), also known as (atopic) eczema, is a common chronic inflammatory skin condition characterized by pruritus. It is a heterogeneous disease with a wide spectrum in clinical presentation, which may change over time. Besides a variety in clinical presentation (e.g. presence of the eczema in the flexures vs. nonflexural eczema), some have described distinct subtypes based on nonclinical features [e.g. presence of filaggrin (FLG) mutations or serum immunoglobulin E (IgE)]. AD is considered both an immunological and skin barrier disorder. The disease is influenced by endogenous factors, i.e. a genetic predisposition, as well as by exposure to environmental factors.¹

In general, the term phenotype is a comprehensive concept and is used in numerous ways in the literature. There is a need for comparability between studies. A phenotype could be defined as a set of features of an individual resulting from the interplay between genetic and environmental factors. Due to its complexity in presentation and pathogenesis, various attempts have been made to classify AD into phenotypes.² Phenotypes within AD can be distinguished based on various features, which could include any static or dynamic feature such as clinical presentation (i.e. morphology and course of disease), or nonclinical features (e.g. based on genetics or immunology).³ The identification of clinically meaningful phenotypes could be a first step to enable stratification of patients in the context of personalised medicine.

The primary objective of this systematic review was to report AD phenotypes, focussing on certain clinical phenotypes, that have been published in the literature and how these were defined, as well as to investigate which patient characteristics were associated with these phenotypes in subsequent analyses. Our secondary objective was to summarize the methodological approaches used to derive the phenotypes. To this point in time, no studies have been undertaken to systematically review the literature and summarize previously defined phenotypes in the field of AD.

Methods

Protocol and registration

The protocol for this systematic review has been published prior to the start of this study.³ In addition, the protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42018087500).⁴ The changes to the protocol are summarized in Appendix S1 (Supporting Information). The study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.⁵

Eligibility criteria

In the context of this systematic review, we have defined phenotype as any subtype or subgroup of AD patients in which associated characteristics were investigated.³ Subgroups of AD patients could be defined based on any feature, including both clinical and nonclinical features. We have included published studies that have a main aim to describe at least one of the following five phenotypic groupings:

- 1) The AD phenotype is defined by disease severity (e.g. mild, moderate-to-severe, severe).
- 2) The AD phenotype is defined by disease trajectory (e.g. early-onset, late-onset).
- 3) The AD phenotype is defined by morphological features (i.e. based on findings at physical examination [e.g. flexural eczema]); and
- 4) The AD phenotype is defined by (history of) eczema herpeticum. In these four phenotypic groupings, the associated characteristics (e.g. FLG mutations) are subsequently investigated per phenotype. For papers that did not define the phenotype by morphological features (see under 3), but instead first determined the phenotype (e.g. based on FLG mutations) in order to describe morphological characteristics in these subgroups, we included as a fifth phenotype:
- 5) The study defines the AD phenotype based on a certain feature (e.g. FLG mutations) in order to investigate morphological characteristics in these phenotypes.

We have excluded studies of localised eczema such as hand eczema, if not mentioned specifically in patients with AD, and other types of eczema such as contact dermatitis and seborrheic dermatitis; literature reviews, case reports and case series; conference abstracts, books and book chapters; and studies on other phenotype categories than defined above (including subgroups based only on age, gender, ethnic populations, presence of triggers, comorbidities, immunology and genetics). Ichthyosis vulgaris, prurigo nodularis and keratosis pilaris in AD patients were considered morphological features.

Search strategy and information sources

A comprehensive literature search strategy was developed in consultation with a clinical librarian. We have searched Ovid EMBASE, Ovid MEDLINE and Web of Science from inception till 12 February 2021. No language restrictions or filters were applied. The Ovid MEDLINE search strategy can be found in Appendix S2 (Supporting Information). In addition, the reference lists from three major review articles were hand-searched for relevant studies.^{1,2,6}

Study selection process

The results of the literature search were uploaded into Covidence online software. All titles and abstracts were screened independently by two reviewers, using a screening tool based on our eligibility criteria. Publications that both reviewers recorded as meeting the inclusion criteria were retrieved for full-text review and excluded when not meeting the criteria. Disagreements were discussed with a second reviewer if necessary. Persistent conflicts were resolved with a senior author. Thereafter, full-text publications were reviewed in duplicate by two separate reviewers. Disagreements were resolved after discussion between the reviewers and with a senior author if necessary.

Data extraction process

Data from each full-text publication were independently extracted by two reviewers (A.B., A.A., R.I., K.F. and J.M.), using a data extraction form designed for this purpose. Discrepancies in data extraction were resolved by discussion if necessary.

Data items

We extracted the following data domains from the included publications using our predesigned data extraction form: study data, disease data and outcome data. The study data comprised the following items: year(s) conducted, study design, setting conducted in, country/countries conducted in, World Health Organization (WHO) region, and the number, age and gender of the participants with (atopic) eczema. The following disease data items were extracted: disease description, diagnostic criteria/codes and disease severity definition. The following outcome data items were extracted: qualitative description of the phenotype(s), proportion of individuals in each phenotype (if relevant), qualitative description of the characteristic(s) (of a priori interest) potentially associated with the phenotype(s), result of the statistical analyses on the association, methodological approach for deriving phenotype(s) and/or investigating the association (including a data-driven approach using statistical techniques, rather than the predefinition of phenotypes, if applicable), and whether controls were included (including the number).

Synthesis of results

The results are reported descriptively. We anticipated that both the phenotype definitions and potentially associated characteristics that are investigated would vary between studies. Therefore, we expected heterogeneity in all outcomes. We have grouped studies into categories where possible and composed evidence tables per phenotype category. If more than one phenotype category was applicable to one study, the publication was grouped into all relevant categories.

Risk of bias assessment

Risk of bias was assessed per study using the critical appraisal checklists for analytical cross-sectional studies, cohort studies

and case-control studies from the Joanna Briggs Institute (JBI), as appropriate.⁷ In the forms, we have treated the described phenotype as the outcome and the description of the potentially associated characteristics under investigation as the exposure. Traffic light tables were composed according to study design and phenotype category to visualize the qualitative results descriptively.

Quality of the evidence

We aimed to use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for assessing the quality of evidence per phenotype category. As we anticipated that the phenotype definitions and potentially associated characteristics would vary between studies, an assessment was made whether the quality of evidence per phenotype category could be investigated.

Results

Search results

We have screened 8511 records and have assessed 675 full-text publications. In total, 186 studies, published between 1966 and 2021, fulfilled the inclusion criteria. Reference searching has yielded 6 additional publications. Figure 1 gives an overview of the study selection process, including reasons for exclusion.

Study overview

Of the included articles, 59% (109/186) was hospital-based (medical specialist setting). Regarding study design, 76% (141/186) was cross-sectional studies. In 7% of studies (13/186), a data-driven approach was used to derive phenotypes, including two studies using existing data-driven phenotypes. The number of included AD patients ranged from seven to 526 808. Ninety-one (49%) publications investigated phenotypes based on disease severity (phenotype group 1). Phenotypes based on disease trajectory (phenotype group 2) were investigated in 56 (30%) studies. Thirty-six (19%) studies investigated morphological characteristics in other phenotypes (phenotype group 5). A morphology-based phenotype (phenotype group 3) and a phenotype of AD patients having eczema herpeticum (phenotype group 4) were investigated in 22 (12%) and 11 (6%) studies respectively. There was an overlap between phenotype categories in 26 studies, with two ($n = 22$) to three ($n = 4$) phenotype categories being investigated in one study. An overview of the study characteristics per study grouped per phenotype category can be found in Table S1a–e (Supporting Information).

Risk of bias

The risk of bias of studies is reported in Table S2a–e (Supporting Information), demonstrating the qualitative results of the JBI critical appraisal checklists according to study design and

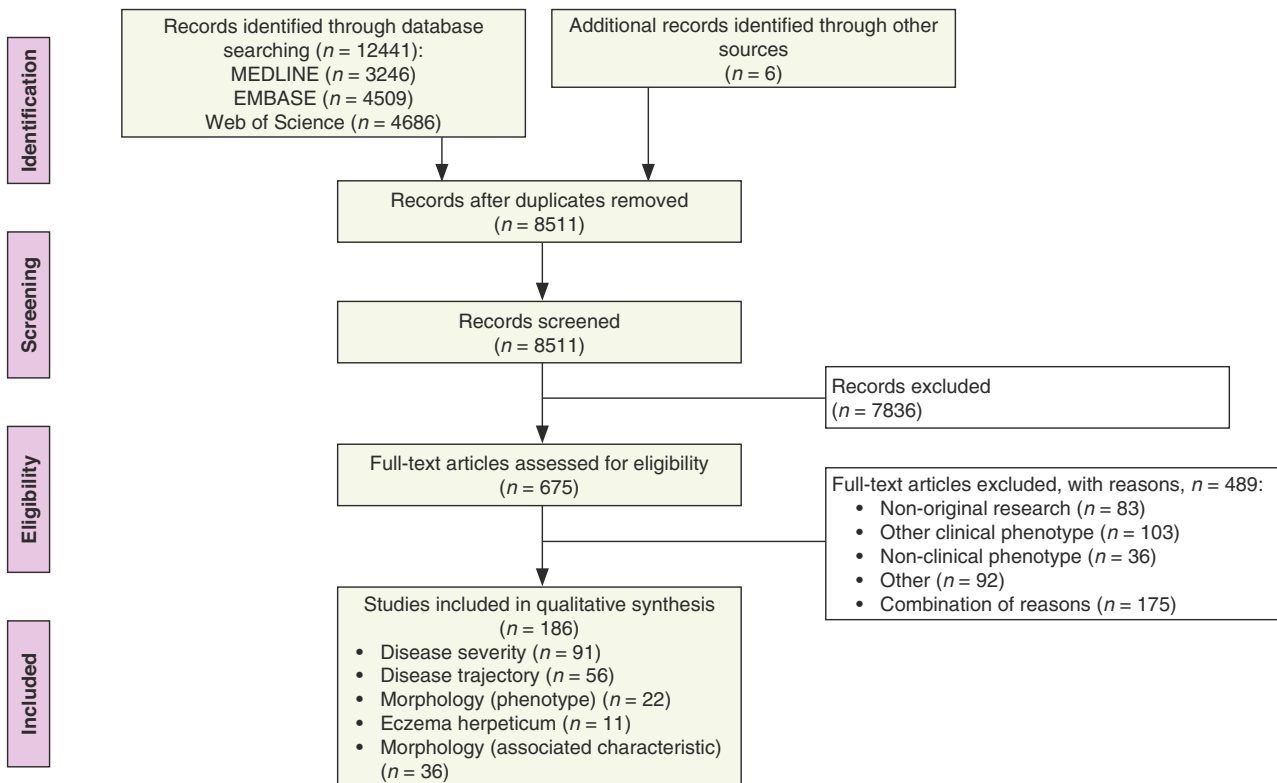


Figure 1 PRISMA flow diagram.

phenotype category. We decided not to give an overall estimation of the risk of bias per paper but to descriptively report the checklist results per paper.

In various papers (30%, 27/91) within the disease severity category (phenotype group 1), no predefined scoring system or severity cut-offs were reported, resulting in the score unclear for outcome in the risk of bias assessment.^{8–10} In many papers (27%, 15/56) on disease trajectories (phenotype group 2), age cut-offs were unclear or it was unclear who assessed the age of onset (i.e. whether it concerned reports by patient, parent or physician).^{11–13} A lack of detail was identified regarding phenotypes based on morphological features and the investigation of morphological characteristics in other phenotypes (phenotype group 3 and 5). Often (in 69%, 41/59), it was unclear who performed the assessment or no criteria or further specifications for the assessment of morphological characteristics were reported (i.e. when characteristics were considered present or not).^{14,15} Overall, in many cross-sectional studies (60%, 84/140), the subjects and setting were not described in sufficient detail.^{16–18} In addition, the absence of inclusion of potentially confounding factors in the analyses of many studies (55%, 102/186) was noteworthy. A major

source of bias across studies related to the two latter factors in the checklists.

Quality of the evidence

We found heterogeneity in the phenotypes and investigated characteristics that were reported in studies and the results of this review are descriptive. Therefore, following discussions with author M.L., an international leading GRADE researcher, assessing the quality of the evidence with GRADE, was considered not relevant.

Study results

An overview of all studies in alphabetical order per phenotype category and details of the results are found in Table S1a–e (Supporting Information). The results of the statistical analyses are summarized per phenotype category and per category of associated characteristics in Appendix S3 (Supporting Information). An overview of all phenotypic groupings and their investigated characteristics can be found in Fig. 2 (graphical abstract).

Phenotypes based on disease severity (phenotype group 1)

Within this phenotype category, 86% (78/91) of studies were

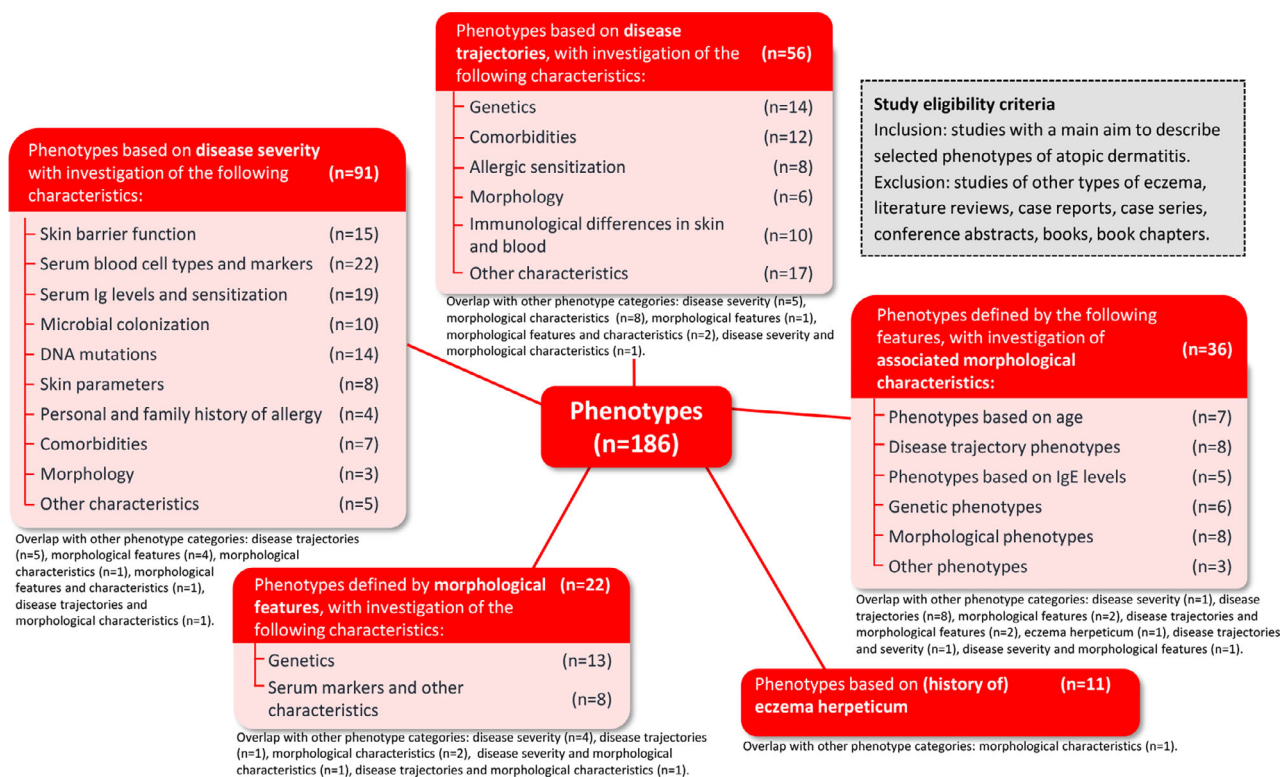


Figure 2 Phenotypes of atopic dermatitis and investigated associated characteristics (Graphical abstract).

cross-sectional, 66% (60/91) was hospital-based only, and in 2% (2/91), a data-driven approach was used. In the studies, the number of included AD patients ranged from seven to 526 808. Regarding WHO region, the majority of studies were conducted in the European Region ($n = 50$, 55%), followed by the Western Pacific Region ($n = 21$, 23%), the Region of the Americas ($n = 16$, 18%) and the African Region and the Eastern Mediterranean Region (both $n = 1$, 1%). Investigated characteristics included the following categories: skin barrier function ($n = 15$),^{19–33} serum blood cell types and markers ($n = 23$),^{9,18,23,34–53} serum Ig levels and sensitization ($n = 15$),^{20,22,25,51,54–64} microbial colonization ($n = 10$),^{15,65–73} DNA mutations ($n = 14$),^{10,51,74–85} skin parameters ($n = 8$),^{32,86–92} personal and family history of allergy ($n = 4$),^{58,93–95} comorbidities ($n = 7$),^{8,51,96–100} morphology ($n = 3$)^{51,93,101} and other characteristics ($n = 5$)^{51,95,102–104} (see Table S1a and Appendix S3, Supporting Information).

The use of different scoring systems for determining disease severity were identified among the included studies (e.g. SCoring Atopic Dermatitis (SCORAD), Eczema Area and Severity Index (EASI)). The SCORAD was most frequently used (in 39 out of 91 studies). Strikingly, we found that even when the same scoring system was used, cut-offs used to make a distinction between, for example, mild, moderate and severe AD differed between studies. For example, in studies, mild AD has been

defined as SCORAD ranging from <15 to <37 points.^{22,33,34,66} The threshold for severe AD ranged from >25 to >50 points.^{25,59,79} In addition, in many articles, no further specification of the basis of the severity definition was given.^{10,15,38,42,44,68,69,89,52,91}

Phenotypes based on disease trajectories (phenotype group 2) Within this phenotype category, 50% (28/56) of studies was cross-sectional, 57% (32/56) was hospital-based only, and in 18% (10/56), a data-driven approach was used. In the studies, the number of included AD patients ranged from nine to 108 703. Most studies were conducted in the European Region ($n = 33/56$, 59%). Thirteen studies (23%) were conducted in the Western Pacific Region, 9 (16%) in the Region of the Americas, and one (2%) in the South-East Asian Region. Investigated characteristics included genetics ($n = 14$),^{11,17,21,51,84,105–113} comorbidities ($n = 12$),^{111,112,114–123} allergic sensitization ($n = 8$),^{12,63,112,124–128} morphology ($n = 6$),^{13,114,121,129–131} immunological differences in skin and blood ($n = 10$)^{16,21,86,91,132–137} and other characteristics ($n = 17$)^{111,112,114,121,124,138–149} (see Table S1b and Appendix S3, Supporting Information).

Many studies which investigated phenotypes based on disease trajectories (including age of onset) and their associated characteristics were cross-sectional studies ($n = 28/56$, 50%;

with predefined phenotypes based on age cut-offs), rather than longitudinal studies ($n = 28/56$, 50%; using for example statistical data-driven approaches). Cross-sectional studies investigating phenotypes based on disease trajectory have the potential of recall bias and a lack of information on temporality. However, in comparison with the other phenotype categories, longitudinal studies were predominantly seen within this category. Early-onset disease was the most reported phenotype ($n = 36/56$, 64%). It predominantly concerned studies in adults retrospectively assessing self-reported early onset of disease. These findings should be interpreted with caution as a previous study has reported that using the question 'Have you had childhood eczema?' to determine age of onset of AD leads to overestimation of the prevalence of childhood AD in adults.¹⁹⁵ The age cut-offs used diverged across studies. For example, early-onset disease was defined using an age cut-off that ranged from 3 months to 8 years. Therefore, use of the term early-onset currently has limited informative value. Besides using age cut-offs in the phenotype definition, inclusion of a maximum/minimum disease duration was added to the definition in five studies (e.g. early-onset disease as within 6 months of disease onset).^{86,91,114,132,137}

Phenotypes defined by morphological features, with subsequent investigation of associated characteristics (phenotype group 3) Within this phenotype category, 95% (21/22) of studies was cross-sectional, 73% (16/22) was hospital-based only, and a data-driven approach was used in none of the studies. In the studies, the number of included AD patients ranged from 21 to 2205. Regarding WHO region, 59% (13/22) of studies was performed in the Western Pacific Region and 41% (9/22) in Region of the Americas and/or the European Region. Thirteen studies investigated genetic characteristics,^{105,108,150–160} and eight studies investigated serum markers and other characteristics^{14,15,22,45,46,101,161,162} (see Table S1c and Appendix S3, Supporting Information).

Phenotypes based on history of eczema herpeticum (phenotype group 4) Within this phenotype category, 91% (10/11) of studies was cross-sectional, 36% (4/11) was hospital-based only (study setting was not reported in 6 studies). In addition, in none of the studies, a data-driven approach was used. In the studies, the number of included AD patients ranged from 35 to 165 199. Nine (82%) of the studies were conducted in the Region of the Americas. One study (9%) was conducted in the European Region and one study (9%) in the Western Pacific Region. Various associated characteristics were investigated^{163–173} (see Table S1d and Appendix S3, Supporting Information). Notably, in most studies, the diagnosis of (history of) eczema herpeticum was confirmed by either anti-HSV antibody titer, PCR, Tzanck smear, immunofluorescence and/or culture test results. These are all

objective assessments rather than a predefinition that could be subject to interpretation.

Phenotypes defined by any feature, with subsequent investigation of associated morphological characteristics (phenotype group 5) Within this phenotype category 83% (30/36) of studies was cross-sectional, 72% (26/36) was hospital-based only, and in none of the studies, a data-driven approach was used. Regarding WHO region, 47% (17/36) of studies was performed in the European Region, 28% (10/36) in the Western Pacific Region, 14% (5/36) in Region of the Americas, 3% (1/36) in the South-East Asian Region and 3% (1/36) in the Eastern Mediterranean Region. In the studies, the number of included AD patients ranged from 31 to 6208. Various phenotype categories were investigated, including phenotypes based on age ($n = 7$),^{93,174–179} disease trajectory ($n = 8$),^{12,13,114,121,129–131,145} IgE levels ($n = 5$),^{126,180–183} genetics ($n = 6$),^{184–189} morphology ($n = 8$)^{14,101,108,131,153,163,190,191} and other phenotypes ($n = 3$)^{51,192,193} (see Table S1e and Appendix S3, Supporting Information).

For phenotypes defined by morphological features and phenotypes defined by any feature with subsequent investigation of associated morphological characteristics, the study region may be relevant. Potential differences in AD morphology by study region have been reported.¹⁹⁶ Therefore, the role of the region where the study took place should be considered. For studies investigating morphology including distribution of AD over the body surface, it became clear that, apart from the reporting of affected body parts, often no further specification was given at all. The reproducibility of these studies is questionable, as specific criteria are unclear. Research shows that variability exists in how people distinguish body parts.¹⁹⁷ Further specification of how body parts are confined or when dermatitis was scored to be present (e.g. using size cut-offs) would have contributed to the quality of these studies.

Discussion

Summary of evidence

We have undertaken a comprehensive analysis of the published literature on phenotype definitions used in literature and have described the characteristics associated with phenotypes. Phenotypes of patients with AD have been identified based on various features, including disease severity, disease trajectories, morphology and predisposition to eczema herpeticum. With this systematic review, we have gained insight on how these phenotype categories are reported in the literature, thereby contributing to developing a better understanding of AD. This systematic review highlights the heterogeneity that currently exists in the phenotyping of the AD population. In the literature, many phenotypes based on many features are described. At the present time, no consensus exists on how these phenotypes of AD should be

defined, and the potential role of phenotypes in guiding both diagnostic and therapeutic management of patients is unknown.

Across the phenotype categories there were both differences and similarities in study characteristics. We identified mostly cross-sectional studies ($n = 141$, 76%) in predominantly hospital-based settings ($n = 109$, 59%). Hospital-based studies could be subject to selection bias due to referral criteria, potentially leading to the identification of other phenotypes than when a population-based approach was used. Therefore, hospital-based studies need to be interpreted cautiously.¹⁹⁴ Phenotypes based on disease severity were most frequently studied ($n = 91$, 49%). The methodological approach for investigating phenotypes differed between studies. Besides the predefinition of a subgroup of patients based on certain features (e.g. cut-offs for age or severity), statistical data-driven approaches were also used to identify phenotypes in the minority of studies ($n = 13$, 7%), for example, by using latent class analysis or cluster analysis. Though these data-driven approaches are only used in a minority of studies aiming to investigate phenotypes, this can be considered a relatively unbiased way to identify phenotypes, in contrast to an approach using an investigator-imposed predefinition. The most frequently used data-driven approach is latent class analysis. Data-driven approaches have the potential to identify patterns that are not obvious to clinical observation. Unfortunately, this only was performed in a small number of studies.

Strengths and limitations

No previous systematic reviews were undertaken to map the current evidence on AD phenotypes in the literature. Librarians were involved in composing a comprehensive and broad search strategy. The protocol of this systematic review was published and preregistered. Moreover, we adhered to PRISMA guidelines in the reporting of this study.

Limitations include that since both the phenotype definitions and the a priori defined characteristics of interest differed between studies, we were unable to pool results and did not use GRADE to assess the quality of evidence. Accordingly, no meta-analyses could be undertaken due to this heterogeneity in study outcomes, and therefore, we have reported on all studies separately in the evidence tables (Table S1a–e, Supporting Information) and Appendix S3 (Supporting Information). Meta-bias resulting from publication bias or selective outcome reporting bias could not be assessed formally because of the qualitative nature of the study. However, both types of bias are deemed unlikely because of our rigorous search and descriptive nature of the studies. Studies were retrieved by our search when the term phenotype or synonyms of phenotype were specifically mentioned. In other words, studies that have used other terminologies (i.e. studies that describe phenotypes, but do not use the terminology phenotype or synonyms of phenotype) could have been missed. A bias for recent studies may have been introduced

by the absence of these terminologies at inception of the used databases. Case reports and case series, for example, describing morphological phenotypes were excluded. Although we report associations between phenotypes and characteristics, these do not prove any causal relationship, and many are based on small sample sizes in hospital-based populations and hence should be interpreted with caution due to the possibility of referral and selection bias. In context of the scoping nature of this systematic review, we did not restrict to a specific study setting, size or confounder adjustment. Lastly, because the term phenotype is used in numerous ways in the literature, we had to define phenotype for consistency, and in the context of this systematic review, we have defined phenotype as a subtype or subgroup of patients with AD. In the context of precision medicine, a semantic distinction with endo(pheno)types would be of interest. It was not feasible to include all potential phenotypic groupings in this study. Therefore, we were forced to make choices on which phenotypes to focus, which resulted in focussing only on the most clinically relevant phenotypes. Excluded phenotype categories include subgroups based only on age, gender, ethnic populations, presence of triggers, (allergic) comorbidities, immunology and genetics.

Implications and recommendations for future research

At the moment, the therapeutic management of AD is generally not based on phenotypes that could reflect potentially relevant differences in characteristics between patients, with the exception of severity. In theory, these differences in phenotypes could be associated with variations in treatment outcome. In the context of personalized medicine, stratification according to phenotype would be of interest to enable investigation of which patients are likely to respond best to certain therapies. In order to facilitate comparative or pooled analyses across studies in the future, phenotypes should be uniformly defined and consistently used. Ideally, researchers should use the same definitions for AD phenotypes in research, similarly to using the same core outcome set for outcome measurements in clinical trials and clinical practice (www.homeforeczema.org/). This core outcome set already includes the recommendation of using the EASI to measure disease severity. A previous study has determined and recommended the following severity strata for EASI: 0: clear, 0.1–5.9: mild, 6.0–22.9: moderate and 23.0–72: severe.¹⁹⁸ We should preferably use the same outcome measurements and cut-offs to describe disease severity phenotypes. Regarding phenotypes based on disease trajectories, we ideally should use the same definitions, e.g. early-onset disease, by using uniform age cut-offs, when using non-data-driven approaches. However, first, we should get a clearer picture of the predictive ability of such cut-offs. As for morphology, it would be desirable to develop (diagnostic) criteria for morphological phenotypes, as current diagnostic criteria for AD do not facilitate the identification of these or phenotypes in general.^{199,200} The current

heterogeneity in phenotyping of AD has demonstrated a need for international harmonization. More research using unbiased data-driven approaches in well-defined, population-based settings should be considered to allow for the identification of phenotypes that are not obvious to clinical observation. Selection of appropriate data-driven techniques should be guided by the nature of the dataset, e.g. whether it is cross-sectional or longitudinal, and by the types of input available (disease activity, severity, clinical presentation etc.). To date, most cross-sectional data-driven techniques have been from the family of cluster analysis, and longitudinal data techniques have been from the family of mixture models such as latent class analysis. Phenotypes identified by a wide range of cross-sectional data may be more richly characterized than phenotypes identified by a smaller range of fewer but longitudinally collected data, but their interpretation may be different. For example, cross-sectional phenotypes may describe clinical AD presentation well but may be less suitable to track the persistence or resolution characteristics that longitudinal phenotypes characterize and vice versa. Whatever the method, the resulting phenotypes should be interpreted in context of the demographic characteristics (e.g. age, sex, ethnicity and geographical region) of the population represented by the sample used to derive them, i.e. not assumed to be applicable to populations not included in the sample. Phenotype studies should also be replicated in independent populations to investigate the stability of the identified phenotypes. In addition, it would be of interest to investigate phenotypes based on allergic comorbidities, since we apprehend AD as part of a larger group of diseases with TH2 inflammation skewing. Lastly, the identification of clinically meaningful phenotypes in the context of treatment outcome should be pursued, by investigating therapeutic effectiveness and safety in patients stratified according to phenotype.

Conclusions

This systematic review has identified a lack in the uniform and consistent use of phenotypes of AD across studies. We have presented an overview of the phenotype definitions used in literature for disease severity, disease trajectory, morphology and eczema herpeticum. In addition, we describe characteristics reported to be associated with these phenotypes, and other phenotypes with subsequent investigation of associated morphological characteristics. Heterogeneity was observed in phenotype definitions used and in associated characteristics investigated within the same phenotypic grouping. Further research applying a consistent and uniform use of phenotype definitions and data-driven data approaches are recommended. The identification of clinically meaningful phenotypes and insights into underlying endotypes has the potential to improve therapeutic strategies, by working towards personalized medicine and ultimately leading to the improvement of care for this condition.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

References

- 1 Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. *Lancet* 2020; **396**: 345–360.
- 2 Bieber T. Atopic dermatitis 2.0: from the clinical phenotype to the molecular taxonomy and stratified medicine. *Allergy* 2012; **67**: 1475–1482.
- 3 Mulick AR, Allen V, Williams HC *et al.* Classifying atopic dermatitis: protocol for a systematic review of subtypes (phenotypes) and associated characteristics. *BMJ Open* 2018; **8**: e023097.
- 4 PROSPERO protocol. URL https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=87500 (last accessed: 14 Dec 2020).
- 5 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009; **62**: 1006–1012.
- 6 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**: s58–S64.
- 7 Joanna Briggs Institute critical appraisal tools. URL <https://joannabriggs.org/critical-appraisal-tools> (last accessed: 14 December 2020).
- 8 Arima M, Shimizu Y, Sowa J *et al.* Psychosomatic analysis of atopic dermatitis using a psychological test. *J Dermatol* 2005; **32**: 160–168.
- 9 Jenerowicz D, Czarnecka-Operacz M, Silny W. Peripheral blood eosinophilia in atopic dermatitis. *Acta Dermatovenerol Alp Panon Adriat* 2007; **16**: 47–52.
- 10 Lacy K, Archer C, Wood N, Bidwell J. Association between a common IL10 distal promoter haplotype and IgE production in individuals with atopic dermatitis. *Int J Immunogenet* 2009; **36**: 213–216.
- 11 Dezman K, Korosec P, Rupnik H, Rijavec M. SPINK5 is associated with early-onset and CHI3L1 with late-onset atopic dermatitis. *Int J Immunogenet* 2017; **44**: 212–218.
- 12 Garmhausen D, Hagemann T, Bieber T *et al.* Characterization of different courses of atopic dermatitis in adolescent and adult patients. *Allergy* 2013; **68**: 498–506.
- 13 Yazganoglu KD, Ozkaya E. Non-typical morphology and localization in Turkish atopic dermatitis patients with onset before the age of 18 years. *Indian J Dermatol Venereol Leprol* 2011; **77**: 23–27.
- 14 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**: 167–177.
- 15 Kaga M, Sugita T, Nishikawa A, Wada Y, Hiruma M, Ikeda S. Molecular analysis of the cutaneous Malassezia microbiota from the skin of patients with atopic dermatitis of different severities. *Mycoses* 2011; **54**: e24–e28.

- 16 Hagendorens MM, Ebo DG, Bridts CH, Water LV, De Clerck LS, Stevens WJ. Prenatal exposure to house dust mite allergen (Der p 1), cord blood T cell phenotype and cytokine production and atopic dermatitis during the first year of life. *Pediatr Allergy Immunol* 2004; **15**: 308–315.
- 17 Greisenegger EK, 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**: 607–610.
- 18 Dworzak MN, Froschl G, Printz D *et al.* Skin-associated lymphocytes in the peripheral blood of patients with atopic dermatitis: signs of subset expansion and stimulation. *J Allergy Clin Immunol* 1999; **103**: 901–906.
- 19 Jung M, Choi J, Lee SA, Kim H, Hwang J, Choi EH. Pyrrolidone carboxylic acid levels or caspase-14 expression in the corneocytes of lesional skin correlates with clinical severity, skin barrier function and lesional inflammation in atopic dermatitis. *J Dermatol Sci* 2014; **76**: 231–239.
- 20 Addor FAS, Takaoka R, Rivitti EA, Aoki V. Atopic dermatitis: correlation between non-damaged skin barrier function and disease activity. *Int J Dermatol* 2012; **51**: 672–676.
- 21 Flohr C, England K, Radulovic S *et al.* Filaggrin loss-of-function mutations are associated with early-onset eczema, eczema severity and transepidermal water loss at 3 months of age. *Br J Dermatol* 2010; **163**: 1333–1336.
- 22 Flohr C, Perkin M, Logan K *et al.* Atopic dermatitis and disease severity are the main risk factors for food sensitization in exclusively breastfed infants. *J Invest Dermatol* 2014; **134**: 345–350.
- 23 Furue M, Matsumoto T, Yamamoto T *et al.* Correlation between serum thymus and activation-regulated chemokine levels and stratum corneum barrier function in healthy individuals and patients with mild atopic dermatitis. *J Dermatol Sci* 2012; **66**: 60–63.
- 24 Sakurai K, Sugiura H, Matsumoto M, Uehara M. Occurrence of patchy parakeratosis in normal-appearing skin in patients with active atopic dermatitis and in patients with healed dermatitis: a cause of impaired barrier function of the atopic skin. *J Dermatol Sci* 2002; **30**: 37–42.
- 25 Mocsai G, Gaspar K, Nagy G *et al.* Severe skin inflammation and filaggrin mutation similarly alter the skin barrier in patients with atopic dermatitis. *Br J Dermatol* 2014; **170**: 617–624.
- 26 Sugawara T, Kikuchi K, Tagami H, Aiba S, Sakai S. Decreased lactate and potassium levels in natural moisturizing factor from the stratum corneum of mild atopic dermatitis patients are involved with the reduced hydration state. *J Dermatol Sci* 2012; **66**: 154–159.
- 27 O'Regan GM, Kemperman PM, Sandilands A *et al.* Raman profiles of the stratum corneum define 3 filaggrin genotype-determined atopic dermatitis endophenotypes. *J Allergy Clin Immunol* 2010; **126**: 574–580.e1.
- 28 Kezic S, O'Regan GM, Yau N *et al.* Levels of filaggrin degradation products are influenced by both filaggrin genotype and atopic dermatitis severity. *Allergy* 2011; **66**: 934–940.
- 29 Shen CP, Zhao MT, Jia ZX, Zhang JL, Jiao L, Ma L. Skin ceramide profile in children with atopic dermatitis. *Dermatitis* 2018; **29**: 219–222.
- 30 Verzeaux L, Vyumvuhore R, Boudier D *et al.* Atopic skin: *in vivo* Raman identification of global molecular signature, a comparative study with healthy skin. *Exp Dermatol* 2018; **27**: 403–408.
- 31 Toncic RJ, Kezic S, Jakasa I *et al.* Filaggrin loss-of-function mutations and levels of filaggrin degradation products in adult patients with atopic dermatitis in Croatia. *J Eur Acad Dermatol Venereol* 2020; **34**: 1789–1794.
- 32 Biagini Myers JM, Sherenian MG, Baatyrbek Kyzy A *et al.* Events in normal skin promote early-life atopic dermatitis—the MPAACH cohort. *J Allergy Clin Immunol Pract* 2020; **8**: 2285–93.e6.
- 33 Montero-Vilchez T, Segura-Fernandez-Nogueras MV, Perez-Rodriguez I *et al.* Skin barrier function in psoriasis and atopic dermatitis: transepidermal water loss and temperature as useful tools to assess disease severity. *J Clin Med* 2021; **10**: 359.
- 34 Batmaz SB. Simple markers for systemic inflammation in pediatric atopic dermatitis patients. *Indian J Dermatol* 2018; **63**: 305–310.
- 35 de Oliveira TT, Orfali RL, de Lollo C *et al.* Impaired CD23 and CD62L expression and tissue inhibitors of metalloproteinases secretion by eosinophils in adults with atopic dermatitis. *J Eur Acad Dermatol Venereol* 2016; **30**: 2072–2076.
- 36 Okano-Mitani H, Ikai K, Imamura S. Leukotriene A4 hydrolase in peripheral leukocytes of patients with atopic dermatitis. *Arch Dermatol Res* 1996; **288**: 168–172.
- 37 McPherson T, Sherman VJ, Aslam A *et al.* Filaggrin null mutations associate with increased frequencies of allergen-specific CD4+ T-helper 2 cells in patients with atopic eczema. *Br J Dermatol* 2010; **163**: 544–549.
- 38 Schultz Larsen F, Grunnet N. Lymphocyte transformation tests and subpopulations of lymphocytes in a population-based material of atopic dermatitis in twins. *Scand J Immunol* 1985; **21**: 375–381.
- 39 Mladonna A, Tedeschi A, Leggieri E *et al.* Characterization of T cell subsets in patients with atopic dermatitis using OKT monoclonal antibodies. *Ann Allergy* 1985; **54**: 321–324.
- 40 Seneviratne SL, Jones L, Bailey AS, Black AP, Ogg GS. Severe atopic dermatitis is associated with a reduced frequency of IL-10 producing allergen-specific CD4+ T cells. *Clin Exp Dermatol* 2006; **31**: 689–694.
- 41 Takigawa M, Tamamori T, Horiguchi D *et al.* Fc epsilon receptor II/CD23-positive lymphocytes in atopic dermatitis. I. The proportion of Fc epsilon RII+ lymphocytes correlates with the extent of skin lesion. *Clin Exp Immunol* 1991; **84**: 275–282.
- 42 Thompson LF, Mellon MH, Zeiger RS, Spiegelberg HL. Characterization with monoclonal antibodies of T lymphocytes bearing Fc receptors for IgE (T epsilon cells) and IgG (T gamma cells) in atopic patients. *J Immunol* 1983; **131**: 2772–2776.
- 43 Wehrmann W, Reinhold U, Kukul S, Franke N, Uerlich M, Kreysel HW. Selective alterations in natural killer cell subsets in patients with atopic dermatitis. *Int Arch Allergy Appl Immunol* 1990; **92**: 318–322.
- 44 Wehrmann W, Reinhold U, Pawelec G, Wernet P, Kreysel HW. In vitro generation of IFN-gamma in relationship to in vivo concentration of IgE and IgG subclasses and Fc epsilon R/CD23 positive circulating lymphocytes in patients with severe atopic dermatitis (AD). *Acta Derm Venereol Suppl* 1989; **144**: 127–130.
- 45 Kou K, Okawa T, Yamaguchi Y *et al.* Periostin levels correlate with disease severity and chronicity in patients with atopic dermatitis. *Br J Dermatol* 2014; **171**: 283–291.
- 46 Okawa T, Yamaguchi Y, Kou K *et al.* Serum levels of squamous cell carcinoma antigens 1 and 2 reflect disease severity and clinical type of atopic dermatitis in adult patients. *Allergol Int* 2018; **67**: 124–130.
- 47 Uysal P, Avcil S, Neselioglu S, Bicer C, Catal F. Association of oxidative stress and dynamic thiol-disulphide homeostasis with atopic dermatitis severity and chronicity in children: a prospective study. *Clin Exp Dermatol* 2018; **43**: 124–130.
- 48 Galli E, Rocchi L, Carello R, Giampietro PG, Panei P, Meglio P. Serum Vitamin D levels and Vitamin D supplementation do not correlate with the severity of chronic eczema in children. *Eur Ann Allergy Clin Immunol* 2015; **47**: 41–47.
- 49 Hallau J, Hamann L, Schumann RR, Worm M, Heine G. A promoter polymorphism of the vitamin D metabolism gene Cyp24a1 is associated with severe atopic dermatitis in adults. *Acta Derm Venereol* 2016; **96**: 169–172.
- 50 Gayret OB, Nacaroglu HT, Erol M, Sener A. Neutrophil-lymphocyte ratio and the platelet parameters as biomarkers of atopic dermatitis severity in children. *Iran Red Crescent Med J* 2019; **21**: e91594.
- 51 Holm JG, Agner T, Clausen ML, Thomsen SF. Determinants of disease severity among patients with atopic dermatitis: association with components of the atopic march. *Arch Dermatol Res* 2019; **311**: 173–182.
- 52 Nousbeck J, McAleer MA, Hurault G *et al.* MicroRNA analysis of childhood atopic dermatitis reveals a role for miR-451a. *Br J Dermatol* 2021; **184**: 514–523.
- 53 Bergallo M, Accorinti M, Galliano I *et al.* Expression of miRNA155, FOXP3 and RORgamma, in children with moderate and severe atopic dermatitis. *G Ital Dermatol Venereol* 2020; **155**: 168–172.

- 54 Johnson EE, Irons JS, Patterson R, Roberts M. Serum IgE concentration in atopic dermatitis. Relationship to severity of disease and presence of atopic respiratory disease. *J Allergy Clin Immunol* 1974; **54**: 94–99.
- 55 Uehara M. Family background of respiratory atopy: a factor of serum IgE elevation in atopic dermatitis. *Acta Derm Venereol Suppl* 1989; **144**: 78–82.
- 56 Yoshikawa K, Ishii M, Chanoki M et al. Relationship of the severity of atopic dermatitis with nonspecific IgE, serum LDH, eosinophil counts in patients given the anti-allergic agent oxatomide. [Japanese] *Skin Res* 2000; **42**: 276–284.
- 57 Winge MC, Bilcha KD, Lieden A et al. Novel filaggrin mutation but no other loss-of-function variants found in Ethiopian patients with atopic dermatitis. *Br J Dermatol* 2011; **165**: 1074–1080.
- 58 Laske N, Niggemann B. Does the severity of atopic dermatitis correlate with serum IgE levels? *Pediatr Allergy Immunol* 2004; **15**: 86–88.
- 59 Mittermann I, Wikberg G, Johansson C et al. IgE sensitization profiles differ between adult patients with severe and moderate atopic dermatitis. *PLoS One* 2016; **11**: e0156077.
- 60 Sanchez J, Sanchez A, Cardona R. Particular characteristics of atopic eczema in tropical environments. the tropical environment control for chronic eczema and molecular assessment (TECCEMA) cohort study. *An Bras Dermatol* 2017; **92**: 177–183.
- 61 Savolainen J, Lammintausta K, Kalimo K, Viander M. *Candida albicans* and atopic dermatitis. *Clin Exp Allergy* 1993; **23**: 332–339.
- 62 Thijs JL, Strickland I, Bruijnzeel-Koomen CAFM et al. Moving toward endotypes in atopic dermatitis: identification of patient clusters based on serum biomarker analysis. *J Allergy Clin Immunol* 2017; **140**: 730–737.
- 63 Quah PL, Loo EX, Lee GN et al. Clinical phenotype and allergen sensitization in the first 2 years as predictors of atopic disorders at age 5 years. *World Allergy Organ J* 2015; **8**: 33.
- 64 Ercan H, Ispir T, Kirac D et al. Predictors of atopic dermatitis phenotypes and severity: roles of serum immunoglobulins and filaggrin gene mutation R501X. *Allergol Immunopathol* 2013; **41**: 86–93.
- 65 Clausen ML, Edslev SM, Andersen PS, Clemmensen K, Kroghfelt KA, Agner T. *Staphylococcus aureus* colonization in atopic eczema and its association with filaggrin gene mutations. *Br J Dermatol* 2017; **177**: 1394–1400.
- 66 Benito D, Aspiroz C, Gilaberte Y et al. Genetic lineages and antimicrobial resistance genotypes in *Staphylococcus aureus* from children with atopic dermatitis: detection of clonal complexes CC1, CC97 and CC398. *J Chemother* 2016; **28**: 359–366.
- 67 Ong PY, Patel M, Ferdman RM, Dunaway T, Church JA. Association of staphylococcal superantigen-specific immunoglobulin e with mild and moderate atopic dermatitis. *J Pediatr* 2008; **153**: 803–806.
- 68 Semic-Jusufagic A, Bachert C, Gevaert P et al. *Staphylococcus aureus* sensitization and allergic disease in early childhood: population-based birth cohort study. *J Allergy Clin Immunol* 2007; **119**: 930–936.
- 69 Zhang E, Tanaka T, Tajima M, Tsuboi R, Nishikawa A, Sugita T. Characterization of the skin fungal microbiota in patients with atopic dermatitis and in healthy subjects. *Microbiol Immunol* 2011; **55**: 625–632.
- 70 Silva MT, Souza VM, Bragagnoli G, Pereira TG, Malagueno E. Atopic dermatitis and ascariasis in children aged 2 to 10 years. *J Pediatr* 2010; **86**: 53–58.
- 71 Zheng Y, Wang Q, Ma L et al. Alterations in the skin microbiome are associated with disease severity and treatment in the perioral zone of the skin of infants with atopic dermatitis. *Eur J Clin Microbiol Infect Dis* 2019; **38**: 1677–1685.
- 72 Brandwein M, Fuks G, Israel A et al. Identification of a unique *Staphylococcus aureus* ribosomal signature in severe atopic dermatitis. *Br J Dermatol* 2018; **179**: 1222–1224.
- 73 Liu Y, Wang S, Dai W et al. Distinct skin microbiota imbalance and responses to clinical treatment in children with atopic dermatitis. *Front Cell Infect Microbiol* 2020; **10**: 336.
- 74 Ekelund E, Lieden A, Link J et al. Loss-of-function variants of the filaggrin gene are associated with atopic eczema and associated phenotypes in Swedish families. *Acta Dermato-Venereologica* 2008; **88**: 15–19.
- 75 Lopes C, Rocha L, Sokhatska O et al. Filaggrin polymorphism Pro478Ser is associated with the severity of atopic dermatitis and colonization by *Staphylococcus aureus*. *J Invest Allergol Clin Immunol* 2016; **26**: 70–72.
- 76 Sandilands A, Terron-Kwiatkowski A, Hull PR et al. Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. *Nat Genet* 2007; **39**: 650–654.
- 77 Brown SJ, Relton CL, Liao H et al. Filaggrin null mutations and childhood atopic eczema: a population-based case-control study. *J Allergy Clin Immunol* 2008; **121**: 940–946.e3.
- 78 Ibrahim GH, ElTabakh MT, Gomaa AH, Mohamed EA. Interleukin-18 gene polymorphisms in Egyptian patients with allergic diseases. *Am J Rhinol Allergy* 2012; **26**: 385–389.
- 79 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 Invest Allergol Clin Immunol* 2012; **22**: 92–101.
- 80 Martel BC, Litman T, Hald A et al. Distinct molecular signatures of mild extrinsic and intrinsic atopic dermatitis. *Exp Dermatol* 2016; **25**: 453–459.
- 81 Oh DY, Schumann RR, Hamann L, Neumann K, Worm M, Heine G. Association of the toll-like receptor 2 A-16934T promoter polymorphism with severe atopic dermatitis. *Allergy* 2009; **64**: 1608–1615.
- 82 Rafatpanah H, Bennett E, Pravica V et al. Association between novel GM-CSF gene polymorphisms and the frequency and severity of atopic dermatitis. *J Allergy Clin Immunol* 2003; **112**: 593–598.
- 83 Salpietro C, Rigoli L, Miraglia Del Giudice M et al. TLR2 and TLR4 gene polymorphisms and atopic dermatitis in Italian children: a multicenter study. *Int J Immunopathol Pharmacol* 2011; **24**(4 Suppl): 33–40.
- 84 Bradley M, Soderhall C, Luthman H, Wahlgren CF, Kockum I, Nordenskjold M. Susceptibility loci for atopic dermatitis on chromosomes 3, 13, 15, 17 and 18 in a Swedish population. *Hum Mol Genet* 2002; **11**: 1539–1548.
- 85 Pigors M, Common JEA, Wong X et al. Exome sequencing and rare variant analysis reveals multiple Filaggrin mutations in Bangladeshi families with atopic eczema and additional risk genes. *J Invest Dermatol* 2018; **138**: 2674–2677.
- 86 Brunner PM, Israel A, Zhang N et al. Early-onset pediatric atopic dermatitis is characterized by T(H)2/T(H)17/T(H)22-centered inflammation and lipid alterations. *J Allergy Clin Immunol* 2018; **141**: 2094–2106.
- 87 Dyjack N, Goleva E, Rios C et al. Minimally invasive skin tape strip RNA sequencing identifies novel characteristics of the type 2-high atopic dermatitis disease endotype. *J Allergy Clin Immunol* 2018; **141**: 1298–1309.
- 88 Czarnowicki T, Gonzalez J, Shemer A et al. Severe atopic dermatitis is characterized by selective expansion of circulating TH2/TC2 and TH22/TC22, but not TH17/TC17, cells within the skin-homing T-cell population. *J Allergy Clin Immunol* 2015; **136**: 104–115.e7.
- 89 Chan TC, Sanyal RD, Pavel AB et al. Atopic dermatitis in Chinese patients shows TH2/TH17 skewing with psoriasisform features. *J Allergy Clin Immunol* 2018; **142**: 1013–1017.
- 90 Lee JH, Shih YT, Wei ML, Sun CK, Chiang BL. Classification of established atopic dermatitis in children with the *in vivo* imaging methods. *J Biophotonics* 2018; **12**: e201800148.
- 91 Pavel AB, Renet-Yuval Y, Wu JN et al. Tape strips from early-onset pediatric atopic dermatitis highlight disease abnormalities in nonlesional skin. *Allergy* 2021; **76**: 314–325.
- 92 Wang HC, Cui L, Jia Y, Gao Y, Zhang GL, He CF. Application of lipidomics to reveal differences of facial skin surface lipids between atopic dermatitis and healthy infants. *J Cosmet Dermatol* 2020; **19**: 1528–1534.

- 93 Foley P, Zuo YQ, Plunkett A, Marks R. The frequency of common skin conditions in preschool-age children in Australia - Atopic dermatitis. *Arch Dermatol* 2001; **137**: 293–300.
- 94 Torsney P, Blumstein GL. Atopic dermatitis. observations in natural history and prognosis. *J Allergy* 1966; **38**: 41–45.
- 95 Galli E, Maiello N, Cipriani F *et al.* Atopic dermatitis phenotypes in preschool and school-age children: a latent class analysis. *J Investig Allergol Clin Immunol* 2020; **30**: 108–116.
- 96 Lowe KE, Mansfield KE, Delmestri A *et al.* Atopic eczema and fracture risk in adults: a population-based cohort study. *J Allergy Clin Immunol* 2020; **145**: 563–571.e8.
- 97 de Bruin-Weller M, Gadkari A, Auziere S *et al.* The patient-reported disease burden in adults with atopic dermatitis: a cross-sectional study in Europe and Canada. *J Eur Acad Dermatol Venereol* 2020; **34**: 1026–1036.
- 98 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**: 248–257.e16.
- 99 Silverwood RJ, Forbes HJ, Abuabara K *et al.* Severe and predominantly active atopic eczema in adulthood and long term risk of cardiovascular disease: population based cohort study. *BMJ (Clinical Research ed)* 2018; **361**: k1786.
- 100 Simpson EL, Guttman-Yassky E, Margolis DJ *et al.* Association of inadequately controlled disease and disease severity with patient-reported disease burden in adults with atopic dermatitis. *JAMA Dermatol* 2018; **154**: 903–912.
- 101 Lammintausta K, Kalimo K. Does a patient's occupation influence the course of atopic dermatitis? *Acta Dermato Venereol* 1993; **73**: 119–122.
- 102 Ungar B, Pavel AB, Robson PM *et al.* A Preliminary 18F-FDG-PET/MRI study shows increased vascular inflammation in moderate-to-severe atopic dermatitis. *J Allergy Clin Immunol Pract* 2020; **8**: 3500–3506.
- 103 Valenzuela F, Fernandez J, Aroca M *et al.* Gingival crevicular fluid zinc and aspartyl-binding protease profile of individuals with moderate/severe atopic dermatitis. *Biomolecules* 2020; **10**: 1600.
- 104 Wei W, Ghorayeb E, Andria M *et al.* A real-world study evaluating adequacy of Existing Systemic Treatments for patients with moderate-to-severe Atopic Dermatitis (QUEST-AD): baseline treatment patterns and unmet needs assessment. *Ann Allergy Asthma Immunol* 2019; **123**: 381–388.e2.
- 105 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**: 456–463.
- 106 Barker JN, Palmer CN, Zhao Y *et al.* Null mutations in the filaggrin gene (FLG) determine major susceptibility to early-onset atopic dermatitis that persists into adulthood. *J Investig Dermatol* 2007; **127**: 564–567.
- 107 Brown SJ, Sandilands A, Zhao Y *et al.* Prevalent and low-frequency null mutations in the filaggrin gene are associated with early-onset and persistent atopic eczema. *J Invest Dermatol* 2008; **128**: 1591–1594.
- 108 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**: 1165–1169.
- 109 Esparza-Gordillo J, Schaarschmidt H, Liang L *et al.* A functional IL-6 receptor (IL6R) variant is a risk factor for persistent atopic dermatitis. *J Allergy Clin Immunol* 2013; **132**: 371–377.
- 110 Zhao LP, Di Z, Zhang L *et al.* Association of SPINK5 gene polymorphisms with atopic dermatitis in Northeast China. *J Eur Acad Dermatol Venereol* 2012; **26**: 572–577.
- 111 Hu C, Duijts L, Eler NS *et al.* Most associations of early-life environmental exposures and genetic risk factors poorly differentiate between eczema phenotypes: the Generation R Study. *Br J Dermatol* 2019; **181**: 1190–1197.
- 112 Abuabara K, Ye M, McCulloch CE *et al.* Clinical onset of atopic eczema: results from 2 nationally representative British birth cohorts followed through midlife. *J Allergy Clin Immunol* 2019; **144**: 710–719.
- 113 Lou C, Mitra N, Wubbenhorst B *et al.* Association between fine mapping thymic stromal lymphopoietin and atopic dermatitis onset and persistence. *Ann Allergy Asthma Immunol* 2019; **123**: 595–601.e1.
- 114 Megna M, Patruno C, Balato A *et al.* An Italian multicentre study on adult atopic dermatitis: persistent versus adult-onset disease. *Arch Dermatol Res* 2017; **309**: 443–452.
- 115 Roduit C, Frei R, Depner M *et al.* Phenotypes of atopic dermatitis depending on the timing of onset and progression in childhood. *JAMA Pediatrics* 2017; **171**: 655–662.
- 116 Martin PE, Eckert JK, Koplin JJ *et al.* Which infants with eczema are at risk of food allergy? Results from a population-based cohort. *Clin Exp Allergy* 2015; **45**: 255–264.
- 117 Shoda T, Futamura M, Yang L *et al.* Timing of eczema onset and risk of food allergy at 3 years of age: a hospital-based prospective birth cohort study. *J Dermatol Sci* 2016; **84**: 144–148.
- 118 Shen CY, Lin MC, Lin HK, Lin CH, Fu LS, Fu YC. The natural course of eczema from birth to age 7 years and the association with asthma and allergic rhinitis: a population-based birth cohort study. *Allergy Asthma Proc* 2013; **34**: 78–83.
- 119 Wan J, Mitra N, Hoffstad OJ, Gelfand JM, Yan AC, Margolis DJ. Variations in risk of asthma and seasonal allergies between early- and late-onset pediatric atopic dermatitis: a cohort study. *J Am Acad Dermatol* 2017; **77**: 634–640.
- 120 Amat F, Saint-Pierre P, Bourrat E *et al.* Early-onset atopic dermatitis in children: which are the phenotypes at risk of asthma? Results from the ORCA cohort. *PLoS One* 2015; **10**: e0131369.
- 121 Silverberg JI, Vakharia PP, Chopra R *et al.* Phenotypical differences of childhood- and adult-onset atopic dermatitis. *J Allergy Clin Immunol Pract* 2018; **6**: 1306–1312.
- 122 Hu C, Nijsten T, Pasmans SGMA, de Jongste JC, Jansen PW, Duijts L. Associations of eczema phenotypes with emotional and behavioural problems from birth until school age. The Generation R Study. *Br J Dermatol* 2020; **183**: 311–320.
- 123 Hu C, Nijsten T, Van Meel ER *et al.* Eczema phenotypes and risk of allergic and respiratory conditions in school age children. *Clin Transl Allergy* 2020; **10**: 7.
- 124 Loo EX, Shek LP, Goh A *et al.* Atopic dermatitis in early life: evidence for at least three phenotypes? Results from the GUSTO study. *Int Arch Allergy Immunol* 2015; **166**: 273–279.
- 125 Just J, Deslandes-Boutmy E, Amat F *et al.* Natural history of allergic sensitization in infants with early-onset atopic dermatitis: results from ORCA Study. *Pediatr Allergy Immunol* 2014; **25**: 668–673.
- 126 Kulthanan K, Boochangkool K, Tuchinda P, Chularojanamontri L. Clinical features of the extrinsic and intrinsic types of adult-onset atopic dermatitis. *Asia Pac Allergy* 2011; **1**: 80–86.
- 127 Wang LC, Chiang BL. Early-onset-early-resolving atopic dermatitis does not increase the risk of development of allergic diseases at 3 years old. *J Formos Med Assoc* 2020; **119**: 1854–1861.
- 128 Yamamoto-Hanada K, Yang L, Saito-Abe M *et al.* Four phenotypes of atopic dermatitis in Japanese children: a general population birth cohort study. *Allergol Int* 2019; **68**: 521–523.
- 129 Nettis E, Ortoncelli M, Pellacani G *et al.* A multicenter study on the prevalence of clinical patterns and clinical phenotypes in adult atopic dermatitis. *J Investig Allergol Clin Immunol* 2020; **30**: 448–472.
- 130 Dezoteux F, Astrid B, Chuffard M, Drumez E, Azib S, Staumont-Salle D. Atopic dermatitis in elderly adults. *Eur J Dermatol* 2019; **29**: 371–374.
- 131 Guglielmo A, Sechi A, Patrizi A, Gurioli C, Neri I. Head and neck dermatitis, a subtype of atopic dermatitis induced by *Malassezia* spp: clinical aspects and treatment outcomes in adolescent and adult patients. *Pediatr Dermatol* 2021; **38**: 109–114.
- 132 Esaki H, Brunner PM, Renert-Yuval Y *et al.* Early-onset pediatric atopic dermatitis is T(H)2 but also T(H)17 polarized in skin. *J Allergy Clin Immunol* 2016; **138**: 1639–1651.

- 133 Seo E, Yoon J, Jung S, Lee J, Lee BH, Yu J. Phenotypes of atopic dermatitis identified by cluster analysis in early childhood. *J Dermatol* 2018; **06**: 06.
- 134 Semic-Jusufagic A, Gevaert P, Bachert C, Murray C, Simpson A, Custovic A. Increased serum-soluble interleukin-5 receptor alpha level precedes the development of eczema in children. *Pediatr Allergy Immunol* 2010; **21**: 1052–1058.
- 135 Paternoster L, Savenije OEM, Heron J et al. Identification of atopic dermatitis subgroups in children from 2 longitudinal birth cohorts. *J Allergy Clin Immunol* 2018; **141**: 964–971.
- 136 Lee E, Lee SH, Kwon JW et al. Atopic dermatitis phenotype with early onset and high serum IL-13 is linked to the new development of bronchial hyperresponsiveness in school children. *Allergy* 2016; **71**: 692–700.
- 137 McAleer MA, Jakasa I, Hurault G et al. Systemic and stratum corneum biomarkers of severity in infant atopic dermatitis include markers of innate and T helper cell-related immunity and angiogenesis. *Br J Dermatol* 2019; **180**: 586–596.
- 138 Mohrenschrager M, Schafer T, Huss-Marp J et al. The course of eczema in children aged 5–7 years and its relation to atopy: differences between boys and girls. *Br J Dermatol* 2006; **154**: 505–513.
- 139 Soomro MH, Baiz N, Philippat C et al. Prenatal exposure to phthalates and the development of eczema phenotypes in male children: results from the EDEN mother-child cohort study. *Environ Health Perspect* 2018; **126**: 027002.
- 140 West CE, Ryden P, Lundin D, Engstrand L, Tulic MK, Prescott SL. Gut microbiome and innate immune response patterns in IgE-associated eczema. *Clin Exp Allergy* 2015; **45**: 1419–1429.
- 141 Yap GC, Loo EX, Aw M, Lu Q, Shek LP, Lee BW. Molecular analysis of infant fecal microbiota in an Asian at-risk cohort-correlates with infant and childhood eczema. *BMC Res Notes* 2014; **7**: 166.
- 142 Wang M, Karlsson C, Olsson C et al. Reduced diversity in the early fecal microbiota of infants with atopic eczema. *J Allergy Clin Immunol* 2008; **121**: 129–134.
- 143 Nowrouzian FL, Ljung A, Nilsson S, Hesselmar B, Adlerberth I, Wold AE. Neonatal gut colonization by *Staphylococcus aureus* strains with certain adhesins and superantigens is negatively associated with subsequent development of atopic eczema. *Br J Dermatol* 2019; **180**: 1481–1488.
- 144 Roduit C, Frei R, Loss G et al. Development of atopic dermatitis according to age of onset and association with early-life exposures. *J Allergy Clin Immunol* 2012; **130**: 130–136.e5.
- 145 von Kobyletzki LB, Bornehag CG, Breeze E, Larsson M, Lindström CB, Svensson Å. Factors associated with remission of eczema in children: a population-based follow-up study. *Acta Derm Venereol* 2014; **94**: 179–184.
- 146 Steiman CA, Evans MD, Lee KE et al. Patterns of farm exposure are associated with reduced incidence of atopic dermatitis in early life. *J Allergy Clin Immunol* 2020; **146**: 1379–1386.e6.
- 147 McKenzie C, Silverberg JL. The prevalence and persistence of atopic dermatitis in urban United States children. *Ann Allergy Asthma Immunol* 2019; **123**: 173–178.e1.
- 148 Yang SI, Lee SH, Lee SY et al. Prenatal PM2.5 exposure and vitamin D-associated early persistent atopic dermatitis via placental methylation. *Ann Allergy Asthma Immunol* 2020; **125**: 665–673.e1.
- 149 Wan J, Mitra N, Hoffstad OJ, Yan AC, Margolis DJ. Longitudinal atopic dermatitis control and persistence vary with timing of disease onset in children: a cohort study. *J Am Acad Dermatol* 2019; **81**: 1292–1299.
- 150 Weidinger S, Illig T, Baurecht H et al. Loss-of-function variations within the filaggrin gene predispose for atopic dermatitis with allergic sensitizations. *J Allergy Clin Immunol* 2006; **118**: 214–219.
- 151 Chen H, Common JEA, Haines RL et al. Wide spectrum of filaggrin-null mutations in atopic dermatitis highlights differences between Singaporean Chinese and European populations. *Br J Dermatol* 2011; **165**: 106–114.
- 152 Cheng F, Zhao JH, Tang XF et al. Association of the chromosome 11p13.5 variant and atopic dermatitis with a family history of atopy in the Chinese Han population. *Asian Pac J Allergy Immunol* 2016; **34**: 109–114.
- 153 Bremner SE, Hanifin JM, Simpson EL. Clinical detection of ichthyosis vulgaris in an atopic dermatitis clinic: implications for allergic respiratory disease and prognosis. *J Am Acad Dermatol* 2008; **59**: 72–78.
- 154 Zhong WL, Wu X, Yu B et al. Filaggrin Gene Mutation c.3321delA is associated with dry phenotypes of atopic dermatitis in the Chinese Han population. *Chin Med J* 2016; **129**: 1498–1500.
- 155 Li M, Cheng R, Shi M et al. Analyses of FLG mutation frequency and filaggrin expression in isolated ichthyosis vulgaris (IV) and atopic dermatitis-associated IV. *Br J Dermatol* 2013; **168**: 1335–1338.
- 156 Cheng R, Li M, Zhang H et al. Common FLG mutation K4671X not associated with atopic dermatitis in Han Chinese in a family association study. *PLoS One* 2012; **7**: e49158.
- 157 Ono E, Murota H, Mori Y et al. Sweat glucose and GLUT2 expression in atopic dermatitis: implication for clinical manifestation and treatment. *PLoS One* 2018; **13**: e0195960.
- 158 Takahashi A, Murota H, Matsui S et al. Decreased sudomotor function is involved in the formation of atopic eczema in the cubital fossa. *Allergol Int* 2013; **62**: 473–478.
- 159 Yasuda-Sekiguchi F, Shiohama A, Fukushima A et al. Single nucleotide variations in genes associated with innate immunity are enriched in Japanese adult cases of face and neck type atopic dermatitis. *J Dermatol Sci* 2021; **101**: 93–100.
- 160 Li ZZ, Zhong WL, Hu H et al. Aryl hydrocarbon receptor polymorphisms are associated with dry skin phenotypes in Chinese patients with atopic dermatitis. *Clin Exp Dermatol* 2019; **44**: 613–619.
- 161 Yamamoto-Hanada K, Kawakami E, Saito-Abe M et al. Exploratory analysis of plasma cytokine/chemokine levels in 6-year-old children from a birth cohort study. *Cytokine* 2020; **130**: 155051.
- 162 Silverberg JI, Margolis DJ, Boguniewicz M et al. Distribution of atopic dermatitis lesions in United States adults. *J Eur Acad Dermatol Venereol* 2019; **33**: 1341–1348.
- 163 Beck LA, Boguniewicz M, Hata T et al. Phenotype of atopic dermatitis subjects with a history of eczema herpeticum. *J Allergy Clin Immunol* 2009; **124**: 260–269.e1–7.
- 164 Hinz T, Zaccaro D, Byron M et al. Atopic dermo-respiratory syndrome is a correlate of eczema herpeticum. *Allergy* 2011; **66**: 925–933.
- 165 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**: 700–703.
- 166 Bin L, Edwards MG, Heiser R et al. Identification of novel gene signatures in patients with atopic dermatitis complicated by eczema herpeticum. *J Allergy Clin Immunol* 2014; **134**: 848–855.
- 167 Takahashi R, Sato Y, Kurata M, Yamazaki Y, Kimishima M, Shiohara T. Pathological role of regulatory T cells in the initiation and maintenance of eczema herpeticum lesions. *J Immunol* 2014; **192**: 969–978.
- 168 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**: 1403–1407.e4.
- 169 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**: 1591–1600.
- 170 Brocardo CJ, Mahaffey S, Schwarz J et al. Comparative proteomic profiling of patients with atopic dermatitis based on history of eczema herpeticum infection and *Staphylococcus aureus* colonization. *J Allergy Clin Immunol* 2011; **127**: 186–U300.
- 171 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**: 507–513, 13.e1–7.
- 172 Boorgula MP, Taub MA, Rafaels N et al. Replicated methylation changes associated with eczema herpeticum and allergic response. *Clin Epigenetics* 2019; **11**: 122.

- 173 Narla S, Silverberg JI. Association between atopic dermatitis and serious cutaneous, multiorgan and systemic infections in US adults. *Ann Allergy Asthma Immunol* 2018; **120**: 66–72.e11.
- 174 Bohme M, Svensson A, Kull I, Wahlgren CF. Hanifin's and Rajka's minor criteria for atopic dermatitis: which do 2-year-olds exhibit? *J Am Acad Dermatol* 2000; **43**(5 Pt 1): 785–792.
- 175 Bohme M, Svensson A, Kull I, Nordvall SL, Wahlgren CF. Clinical features of atopic dermatitis at two years of age: a prospective, population-based case-control study. *Acta Derm Venereol* 2001; **81**: 193–197.
- 176 Julian-Gonzalez RE, Orozco-Covarrubias L, Duran-McKinster C, Palacios-Lopez C, Ruiz-Maldonado R, Saez-de-Ocariz M. Less common clinical manifestations of atopic dermatitis: prevalence by age. *Pediatr Dermatol* 2012; **29**: 580–583.
- 177 Chu H, Shin JU, Park CO, Lee H, Lee J, Lee KH. Clinical diversity of atopic dermatitis: a review of 5,000 patients at a single institute. *Allergy Asthma Immunol Res* 2017; **9**: 158–168.
- 178 Lee HJ, Cho SH, Ha SJ *et al*. Minor cutaneous features of atopic dermatitis in South Korea. *Int J Dermatol* 2000; **39**: 337–342.
- 179 Guo Y, Zhang H, Liu Q *et al*. Phenotypic analysis of atopic dermatitis in children aged 1–12 months: elaboration of novel diagnostic criteria for infants in China and estimation of prevalence. *J Eur Acad Dermatol Venereol* 2019; **33**: 1569–1576.
- 180 Reefer AJ, Satinover SM, Wilson BB, Woodfolk JA. The relevance of microbial allergens to the IgE antibody repertoire in atopic and nonatopic eczema. *J Allergy Clin Immunol* 2007; **120**: 156–163.
- 181 Breninkmeijer EE, Spuls PI, Legierse CM, Lindeboom R, Smitt JH, Bos JD. Clinical differences between atopic and atopiform dermatitis. *J Am Acad Dermatol* 2008; **58**: 407–414.
- 182 Tanei R. Clinical characteristics, treatments, and prognosis of atopic eczema in the elderly. *J Clin Med* 2015; **4**: 979–997.
- 183 Imayama S, Hashizume T, Miyahara H *et al*. Combination of patch test and IgE for dust mite antigens differentiates 130 patients with atopic dermatitis into four groups. *J Am Acad Dermatol* 1992; **27**: 531–538.
- 184 Meng L, Wang L, Tang H *et al*. Filaggrin gene mutation c.3321delA is associated with various clinical features of atopic dermatitis in the Chinese Han population. *PLoS One* 2014; **9**: e98235.
- 185 On HR, Lee SE, Kim SE *et al*. Filaggrin mutation in Korean patients with atopic dermatitis. *Yonsei Med J* 2017; **58**: 395–400.
- 186 Carson CG, Rasmussen MA, Thyssen JP, Menne T, Bisgaard H. Clinical presentation of atopic dermatitis by filaggrin gene mutation status during the first 7 years of life in a prospective Cohort Study. *PLoS One* 2012; **7**: e48678.
- 187 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**: 440–448.
- 188 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**: 115–120.
- 189 Kim M, Yoo J, Kim J *et al*. Association of FLG single nucleotide variations with clinical phenotypes of atopic dermatitis. *PLoS One* 2017; **12**: e0190077.
- 190 Li ZZ, Zhong WL, Hu H *et al*. Aryl hydrocarbon receptor polymorphisms are associated with dry skin phenotypes in Chinese patients with atopic dermatitis. *Clin Exp Dermatol* 2018; **29**: 29.
- 191 Majeed Al-Razzuqi RA, Al-Jeboori AA, Al-Waiz MM. Acetylation phenotype variation in pediatric patients with atopic dermatitis. *Indian J Dermatol* 2011; **56**: 150–152.
- 192 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**: 637–643.
- 193 Li Y, Xu W, Li LF. Risk factors in outpatients with dermatitis and eczema in tertiary hospitals of china who have clinically suspected bacterial infection. *Biomed Res Int* 2020; **2020**: 7621217.
- 194 Williams HC. Atopic Dermatitis. The Epidemiology, Causes and Prevention of Atopic Eczema. Cambridge University Press, Cambridge, UK, 2000.
- 195 Stenberg B, Lindberg M, Meding B, Svensson A. Is the question 'Have you had childhood eczema?' useful for assessing childhood atopic eczema in adult population surveys? *Contact Dermatitis* 2006; **54**: 334–337.
- 196 Yew YW, Thyssen JP, Silverberg JI. A systematic review and meta-analysis of the regional and age-related differences of atopic dermatitis clinical characteristics. *J Am Acad Dermatol* 2018; **01**: 01.
- 197 Reed C, Harris A, Lodge M, Gaither G. Segmentation of the human body: how does the visual system define body parts? *J Vision* 2017; **17**: 1254.
- 198 Chopra R, Vakharia PP, Sacotte R *et al*. Severity strata for Eczema Area and Severity Index (EASI), modified EASI, Scoring Atopic Dermatitis (SCORAD), objective SCORAD, Atopic Dermatitis Severity Index and body surface area in adolescents and adults with atopic dermatitis. *Br J Dermatol* 2017; **177**: 1316–1321.
- 199 Williams HC, Burney PG, Pembroke AC, Hay RJ, The UK. Working party's diagnostic criteria for atopic dermatitis. III. Independent hospital validation. *Br J Dermatol* 1994; **131**: 406–416.
- 200 Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)* 1980; **92**: 44–47.

Supporting information

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

Table S1. Evidence tables per predefined phenotype category.

Table S2. Qualitative outcomes by the JBI critical appraisal checklists.

Appendix S1. Changes to the original protocol.

Appendix S2. Ovid MEDLINE search strategy.

Appendix S3. Summary of main results per phenotype category and per category of associated characteristics.