Systematic Review on the Definition of Allergic Diseases in Children: The MeDALL Study

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Abstract

Background: During the last decades, a large number of phenotypes and disease classifications of allergic diseases have been proposed. Despite the heterogeneity across studies, no systematic review has been conducted on phenotype classification and the criteria that define allergic diseases. We aimed to identify clinically expressed, population-based phenotypes of allergic diseases and their interrelationships, to explore disease heterogeneity and to evaluate the measurements employed in disease diagnosis. Methods: We conducted a search of MEDLINE up to December 2012, to identify relevant original studies published in the English language that examine at least one objective of this systematic review in subjects aged 0–18 years. The screening of titles and abstracts and the extraction of data were conducted independently by two reviewers. Results: From a total of 13,767 citations, 197 studies met the criteria for inclusion, with 54% being cohort studies. Allergic diseases were studied as a single entity in 55% (109/197) of the studies or in the

Key Words
Phenotype · Disease definition · Asthma · Eczema · Rhinitis · Urticaria · Anaphylaxis · Allergy
context of multimorbidity in 45%. Asthma accounted for 81.7% of the studies examining single diseases. Overall, up to 33 different phenotypes of allergic disease were reported. Transient early, late-onset and persistent wheeze were the most frequently reported phenotypes. Most studies (78%) used questionnaires. The skin-prick test was the preferred measurement of sensitization (64%). Spirometry and bronchial hyperresponsiveness were assessed in one third of the studies, peak flow rate in 8.6% and disease severity in 35%.

**Conclusions:** Studies reporting phenotypes of allergic diseases in children are highly heterogeneous and often lack objective phenotypical measures. A concerted effort to standardize methods and terminology is necessary.

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**Introduction**

Allergic diseases represent one of the most common types of disease globally. They incur a substantial global health burden [1]. Major chronic allergic diseases include rhinitis [2], asthma [3], atopic dermatitis [4], gastrointestinal diseases and diseases induced by food allergy [5].

Allergic diseases are complex multifactorial disorders, with interactions of genetic, environmental and socioeconomic factors determining disease expression and leading to different phenotypes. Several mechanisms are involved, but many patients suffer from IgE-mediated reactions [6]. However, not all sensitized subjects develop clinical symptoms [7] nor are all individuals with allergic diseases sensitized, suggesting that the relationship between the symptoms of allergy and positive IgE sensitization is still not clear [7, 8]. Symptoms often begin early in life, but the clinical phenotypes of allergic diseases vary with age [9], thus increasing their complexity. An important characteristic of complex chronic diseases is their heterogeneity. Heterogeneity of asthma has received increasing attention [10]. On the other hand, allergic diseases tend to aggregate in the same individual as multimorbidity [11, 12] or else follow an atopic march [13].

As in other complex chronic diseases, there are multiple ways of defining and classifying allergic diseases. The use of different classifications and definitions is a cause of misunderstanding between clinicians, epidemiologists and scientists [14]. There is no systematic review summarizing the evidence of phenotypes for the classification and definition of each allergic disease.

The European Union-funded project MedALL (Mechanisms of the Development of ALLergy) aims to generate novel knowledge on the mechanisms of initiation of allergy and to propose early diagnosis, prevention and targets for therapy [15]. We conducted a systematic review in order to identify, describe and assess reports of clinical phenotypes of allergic diseases in the literature and determine the needs for future research. Etiological and mechanistic studies addressing determinants (protective and risk factors) of a disease or condition as well as the mechanisms underlying the diseases were included if they reported relevant information directly related to our study aims.

**Materials and Methods**

**Eligibility Criteria and Literature Search**

The review protocol was prospectively registered (CRD42012002443) with the International Prospective Register of Systematic Reviews (PROSPERO) [16]. This systematic review is reported in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [17].

The methods have been described in detail [18]. Briefly, we performed a search to identify studies conducted on subjects aged 0–18 years, which fulfilled at least 1 of the objectives of our systematic review (online suppl. table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000442414). We included cross-sectional studies, case-control studies, case-series, birth cohorts, other cohorts and intervention studies (clinical controlled trials) that (1) assess the methods used to define and examine allergic diseases from childhood to young adulthood, (2) provide evidence for classification and definitions, and (3) explore multimorbidity or heterogeneity of a disease. We excluded (1) studies with the primary aim of assessing phenotype mechanisms and/or etiology (including omics studies) but not providing direct and relevant information about phenotype classification, validation, heterogeneity or the interrelationships between phenotypes (overlap and comparability), (2) studies using unsupervised statistical methods (e.g. any type of clustering or latent class analysis), (3) case reports, (4) ecological studies and (5) experimental studies involving either animals or cell cultures or both.

In addition, eligible original articles were retrieved and their reference lists were searched for additional articles. We restricted the search to English language publications. Some studies which were not retrieved were added by the panel of experts.

Study Selection

Study selection was performed in two stages previously described [16, 18]. The first step was the screening of titles. Two independent reviewers conducted title scans in a parallel fashion.

The second step was the screening of abstracts, which were reviewed by a panel. Prior to this, a pilot test to assess screening validity was conducted in order to ensure that all reviewers understood the protocol, its objectives and the defined inclusion and exclusion criteria. For this purpose, we selected 40 abstracts to be classified as ‘included’, ‘excluded’ or ‘unclear’ (if in doubt). Following the report of the results of the pilot test and discussion in the form of meetings or telephone calls, all reviewers were confident enough to score the abstracts. All abstracts were reviewed by two reviewers independently. Disagreements were resolved by referral to a third reviewer.

Data Extraction

The reviewers reviewed the full texts of all selected publications prior to data extraction. A predesigned data extraction form was developed and two reviewers independently extracted data from the texts in full, with disagreements being resolved by means of discussion among investigators (data extraction form; online suppl. fig. S1). To provide a technological platform for the systematic review, the BioXM environment was used [19].

Quality Assessment and Data Synthesis

We did not assess the quality of the studies due to the descriptive nature of this review, which also covers a wide range of study types. We used STATA v12.0 software (StataCorp., College Station, Tex., USA) to conduct the analyses.
Results

The electronic database search returned 13,676 records. Figure 1 describes the flow of information through the different phases of the systematic review. We conducted a comprehensive manual search of the reference lists of included studies that identified 91 additional records. Of these, 545 fulfilled the criteria for full-text review and 197 met the criteria for inclusion (online suppl. table S2). Of the 197 included studies published between 1972 and 2013, 194 were performed in a single country (out of 34 countries) One was conducted in Africa, 12 in Asia, 24 in Australasia and Oceania, 27 in America (21 in North America), 35 in the UK and 95 in other European countries (online suppl. fig. S2). Three were international studies.

Type of Studies and Methods

The studies assessing single disease entities mainly explored heterogeneity between phenotypes (86/109; 78.9%) and appraised methods (26/109; 23.9%; table 1). They were classified into 5 categories, i.e. those (1) describing phenotypes, (2) validating phenotypes, (3) examining prognosis, (4) assessing treatment response and (5) involving other investigations. The selected studies mainly provided a description of phenotypes or evaluated disease prognosis. Validation of phenotypes was seldom undertaken.

Asthma was mainly studied as a single disease entity, whereas the other allergic diseases were mainly studied in the context of multimorbidity (table 2).

Cohorts were the most common study design (107/197; 54.3%) followed by cross-sectional studies (56/197; 28.4%; table 2).

Most studies (144/197; 73.1%) used both questionnaires and objective measurements (e.g. IgE sensitization, lung function testing and biomarkers) to identify phenotypes, but 6 were exclusively questionnaire-based and 42 used objective measurements only. Questionnaires were mostly self-administered or administered in a face-to-face manner (i.e. by personal interview).

Classification and Definition of Allergic Disease Phenotypes

Disease Phenotypes

Thirty-three different phenotypes of allergic diseases were found (table 3a, b). The classification of phenotypes is based on 7 defining traits: symptoms with or without a temporal pattern, triggers, atopy, inflammation, disease severity, treatment response and multimorbidity (online suppl. tables S3–S10). Only asthma/wheeze phenotypes have been described according to inflammation and treatment response. Asthma and food allergy are the only phenotypes described according to triggers. Other terms related to the defined phenotypes are listed in online supplementary table S11.

Assessment of IgE Sensitization

Almost 70% of the studies reported a parental history of atopy. Skin-prick tests, particularly to inhalant allergens, were carried out in 64.0% of the studies. Serum-specific IgE sensitization to either food or inhalant allergens were assessed in 34.0% of the studies and 47.2% as-
sessed total IgE. The patch test (4.1%) was hardly used (table 4), i.e. ranging from 1.8% of the studies examining asthma to 11.9% of the studies examining food allergy (online suppl. table S3).

Assessment of Lung Function and Bronchial Hyperresponsiveness

Spirometry and bronchial hyperresponsiveness (BHR) were used in 36.1% of the studies examining asthma phenotypes as a single disease and in 30.0% assessing it in a context of multimorbidity (online suppl. table S3). The preferred method to assess BHR was methacholine (in 39.0%) followed by histamine inhalation challenge (in 32.2%). Peak flow was used in only 8.6% of the studies. Other tests were used to measure lung function to detect abnormal pulmonary function in preschool wheezers (online suppl. table S4): partial expiratory flow-volume curves with the chest compression technique [20], respiratory resistance (Rrs6) with the forced oscillatory technique (FOT) and the transcutaneous oxygen (PTCO₂) technique [21], baseline airways resistance by the interrupter technique (Rint) [22, 23], tidal flow volume loops and airways obstruction by time-to-reach peak flow to total-expiratory time (tPTEF/TE) measurement [24], impulse oscillometry bronchodilator response (IOS-BDR) tests [25], multiple-breath wash-out indices, i.e. lung clearance index (LCI) and conductive airways ventilation inhomogeneity [S(cond)] and specific airways resistance [sR(aw)] measured by means of plethysmograph [26, 27] assessment of disease severity.

Disease severity was examined in nearly 35% of the studies, i.e. ranging from 14.3% that examined urticaria and anaphylaxis to 39.8% investigating eczema (online suppl. table S3).

### Discussion

**Summary of Main Findings**

This systematic review has identified great heterogeneity across studies with regard to approaches, methods and allergic phenotypes. Most of the studies included are cohort or cross-sectional studies. Most often, information has been collected using both questionnaires and objective measurements. Most studies aim to describe phenotypes and/or explore heterogeneity within phenotypes and, to a lesser extent, assess disease prognosis and/or explore the interrelationships between phenotypes. Hardly any of the studies validate phenotypes or appraise methods to better define these. Thirty-three phenotypes are identified and defined according to 7 defining traits. Asthma is the most common disease entity studied, accounting for 16 phenotypes. Multimorbidity or comorbidity with other allergic diseases is assessed in half of the cases, most often as a risk factor for asthma. The most common phenotypes are those using temporal patterns of

### Table 2. Distribution of studies included according to their consideration of diseases singly or in multimorbidity, and the study design

<table>
<thead>
<tr>
<th></th>
<th>Asthma</th>
<th>Rhinitis</th>
<th>Eczema</th>
<th>Food allergy</th>
<th>Urticaria</th>
<th>Anaphylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single disease</td>
<td>89</td>
<td>1</td>
<td>12</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Multimorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 diseases</td>
<td>17</td>
<td>8</td>
<td>13</td>
<td>7</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>3 diseases</td>
<td>37</td>
<td>34</td>
<td>36</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4 diseases</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>13</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5 diseases</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>6 diseases</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Not examined</td>
<td>27</td>
<td>127</td>
<td>109</td>
<td>155</td>
<td>183</td>
<td>190</td>
</tr>
<tr>
<td>Study design</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case series</td>
<td>9 (5.3)</td>
<td>4 (5.7)</td>
<td>5 (5.7)</td>
<td>5 (11.9)</td>
<td>3 (21.4)</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Case-control</td>
<td>12 (7.1)</td>
<td>3 (4.3)</td>
<td>4 (4.6)</td>
<td>3 (7.1)</td>
<td>2 (14.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Clinical trial</td>
<td>4 (2.4)</td>
<td>0 (0)</td>
<td>2 (2.3)</td>
<td>2 (4.8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cohort</td>
<td>95 (55.9)</td>
<td>41 (58.6)</td>
<td>54 (61.4)</td>
<td>22 (52.4)</td>
<td>7 (50.0)</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>50 (29.4)</td>
<td>22 (31.4)</td>
<td>23 (26.1)</td>
<td>10 (23.8)</td>
<td>2 (14.3)</td>
<td>1 (14.3)</td>
</tr>
</tbody>
</table>

Data are expressed as n (%). * The number of studies not examining the specific allergic disease.
Table 3. Data on the 33 phenotypes of allergic disease identified in our review

<table>
<thead>
<tr>
<th>Symptom or Phenotype</th>
<th>Symptoms with/without temporal pattern</th>
<th>Factors/Triggers</th>
<th>IgE sensitization</th>
<th>Inflammation</th>
<th>Severity</th>
<th>Treatment response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asthma and/or wheeze</strong></td>
<td>1.1. transient early wheeze 1.2. late-onset wheeze 1.3. persistent wheeze 2.1. acute asthma 2.2. stable asthma 3. chronic (persistent) asthma 4. intermittent asthma/wheeze</td>
<td>5.1. multitrigger wheeze 5.2. episodic (viral) wheeze 6.1. respiratory syncytial virus-induced wheeze 6.2. respiratory syncytial virus-induced bronchiolitis 7.1. Alternaria-positive asthma 7.2. Alternaria-negative asthma 8. solitary exercise-induced bronchoconstriction</td>
<td>9.1. atopic asthma 9.2. nonatopic asthma 10.1. monosensitized asthma 10.2. polysensitized asthma</td>
<td>11.1. eosinophilic asthma 11.2. neutrophilic asthma 11.3. mixed granulocytic asthma 11.4. paucigranulocytic asthma</td>
<td>12. asthma/wheeze severity 13. severe intermittent wheeze</td>
<td>14.1. steroid-sensitive asthma 14.2. steroid-insensitive asthma 15. difficult-to-treat asthma 16. well-controlled asthma</td>
</tr>
<tr>
<td><strong>Eczema/AD</strong></td>
<td>17.1. persistent eczema 17.2. early-onset intermittent eczema 17.3. late-onset intermittent eczema</td>
<td>–</td>
<td>18. allergic contact dermatitis 19.1. extrinsic AE 19.2. intrinsic AE</td>
<td>–</td>
<td>20. AD severity –</td>
<td></td>
</tr>
<tr>
<td><strong>Rhinitis/AR</strong></td>
<td>21.1. seasonal rhinoconjunctivitis 21.2. perennial rhinoconjunctivitis (upper-airway allergy)</td>
<td>food/inhalant allergens: 22.1. rhinitis without sensitization to inhalant allergens 22.2. rhinitis with sensitization to inhalant allergens</td>
<td>22.1. rhinitis without sensitization to inhalant allergens 22.2. rhinitis with sensitization to inhalant allergens 23.1. AR 23.2. nonallergic rhinitis</td>
<td>–</td>
<td>24. chronic rhinitis –</td>
<td></td>
</tr>
<tr>
<td><strong>FA</strong></td>
<td>25.1. transient FHS 25.2. intermittent FHS 25.3. late-onset FHS 25.4. persistent FHS</td>
<td>26. CMA 27. peanut allergy 28. wheat allergy 29.1. clinically reactive to all forms of milk 29.2. tolerant to heated milk products 29.3. outgrown milk allergy 30.1. CMA immediate reactors 30.2. delayed reactors (to cow’s milk challenge)</td>
<td>31.1. IgE-mediated CMA/FA 31.2. non-IgE-mediated CMA/FA</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Urticaria</strong></td>
<td>32.1. single-episode acute 32.2. recurrent acute</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>33.1. acute 33.2. chronic</td>
<td>–</td>
</tr>
</tbody>
</table>

There is an ARIA classification (intermittent rhinitis and persistent rhinitis) that we did not find in our systematic review, but we included a study [74] that assessed intermittence and persistence as a way of grading disease severity. AD = Atopic dermatitis; AE = atopic eczema; CMA = cow’s milk allergy; FA = food allergy; FHS = food hypersensitivity.
wheezing, particularly transient early, late-onset and persistent wheeze. We revealed a major lack of an integrated framework for phenotype identification and reporting.

Strengths and Limitations
This systematic review is, to our knowledge, the first to comprehensively assess how allergic diseases in children have been classified and defined. The search strategy, run from the inception, was comprehensive in identifying all relevant papers. In addition, bibliographies from the studies that met the inclusion criteria were searched, leading to large numbers of articles being reviewed. This was thus the first attempt to formally characterize the variability of these terms in the literature. Moreover, it was conducted by an international and multidisciplinary panel of experts in the field.

The search was restricted to the MEDLINE database and only papers written in English were reviewed. However, it is unlikely that we missed studies that could have added information. The studies selected were conducted mostly in developed countries, and they describe phenotypes which may differ from those of developing countries.

As the number of citations retrieved was so large, we considered using text-mining techniques to shorten the list of potentially eligible studies. Unfortunately, this method was found not to be effective (online suppl. Discussion).

The MEDLINE search was completed in December 2012 and new studies on the atopic march and food allergy have been published recently [28–32].

We did not consider studies that classified diseases using cluster analyses because our review focuses on a pri-


tori defined phenotypes. We thus omitted phenotypes defined by hypothesis-free statistical analysis. We excluded studies which did not provide direct and relevant information about phenotype classification, validation, heterogeneity or the interrelationships between phenotypes (overlap and comparability). However, studies assessing etiology and mechanisms (e.g. protective and risk factors and underlying pathophysiological mechanisms of diseases) were included if they provided information directly related to the aims of the review. In addition, some studies [33–35] were identified for inclusion in the review but were not picked up by our search strategy. Our panel of experts was large and multidisciplinary, but it is possible that a few studies of interest were not identified.

Methodology Used to Identify Allergic Phenotypes
The relationship between patterns of asthma symptoms and objective measurements is poorly defined in pediatric asthma [35]. In contrast, for atopic eczema, major efforts have been made to standardize and validate a core set of outcome measurements as well as increase the quality of outcomes research in dermatology [36]. Only 1 study [37] examines objective measurements (nasal eosinophilia and nasal airway patency) in young children with allergic rhinitis (AR) and nonallergic rhinitis, finding them useful for distinguishing the 2 phenotypes. Very few studies appraise methods for defining the phenotypes of urticaria and anaphylaxis [38–40].

Objective tests are needed for confirming asthma, including spirometry, methacholine and hypertonic saline provocation challenge tests and the measurement of exhaled nitric oxide (eNO). These tests measure different aspects of the same disease, so when they are correlated

Table 3 (continued)

<table>
<thead>
<tr>
<th>Description of comorbid phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asthma and/or wheeze</strong></td>
</tr>
<tr>
<td>Wheezing with rhinoconjunctivitis; wheezing with rhinitis</td>
</tr>
<tr>
<td>Asthma without allergy; asthma with allergy (hay fever, rhinitis, dermatitis and neurodermatitis)</td>
</tr>
<tr>
<td>AE + EIA; AD and current asthma; AD and wheeze; eczema-asthma syndrome</td>
</tr>
<tr>
<td><strong>Eczema/AD</strong></td>
</tr>
<tr>
<td>AE + EIA; AD and current asthma; AD and wheeze; eczema-asthma syndrome</td>
</tr>
<tr>
<td>FA and AE, AD with food hypersensitivity, transient FA + AD, persistent FA + AD</td>
</tr>
<tr>
<td>AD + comorbidities (asthma, allergic rhinoconjunctivitis and urticaria)</td>
</tr>
<tr>
<td><strong>Rhinitis/AR</strong></td>
</tr>
<tr>
<td>Wheezing with rhinoconjunctivitis; wheezing with rhinitis</td>
</tr>
<tr>
<td><strong>FA</strong></td>
</tr>
<tr>
<td>FA and AE; AD with food hypersensitivity; transient FA + AD; persistent FA + AD; oral allergy syndrome</td>
</tr>
<tr>
<td><strong>Urticaria</strong></td>
</tr>
<tr>
<td>Urticaria with AD; urticaria without AD/eczema</td>
</tr>
</tbody>
</table>

AD = Atopic dermatitis; AE = atopic eczema; EIA = exercise-induced asthma; FA = food allergy.
with one another, the evidence is conflicting [41]. Although lung function has been included in studies describing wheezing and asthma phenotypes in preschool and school-aged children [20–27, 42–44] among others, its limited availability in routine clinical practice may have limited the number of phenotypes reported. Despite the importance of disease severity in the characterization of diseases into phenotypes, only a third of the studies examined this issue. The characteristics of severe asthma phenotypes in adults may be evaluated using age at onset, measurements of lung eosinophils (usually in induced sputum) and levels of atopy [45]. In asthmatic children, blood eosinophilia and IgE sensitization (skin tests or blood testing) values are unknown, although some recent studies propose that component IgE levels may be of interest in rhinitis and asthma [46]. In atopic dermatitis, a series of measurements can be used to assess severity [47]. There is an urgent need to validate tests for determining the severity of individual allergic diseases and those occurring in the context of multimorbidity.

Less than 25% of the studies include sociodemographic variables as risk factors or effect modifiers to explain causal pathways of asthma and allergic diseases. Hence, the associations between phenotypes and health inequalities have not been subjected to enough study.

### Discussion of Findings

#### Asthma

The existence of a broad variety of reported asthma phenotypes raises a number of issues (online suppl. Discussion). First, we lack a standardized classification that has been reached by consensus. The result is a large degree of variability in research and clinical practice. Second, there is an insufficient validation of asthma phenotypes. There is a need for characterization and replication studies. Third, a substantial overlap occurs among phenotypes [10], particularly because specific phenotypes are not always stable and there is substantial interaction between phenotypes. Fourth, the severity of asthma has been insufficiently approached and studies using sputum may be of importance.

#### Rhinitis

Although it has been proposed that AR affects an increasing proportion of preschool children, there is a paucity of data regarding its epidemiology [26, 48]. The symptoms of rhinitis are ill-defined, possibly because they were reported by the caregivers. AR is not better identified, and also viral triggers may interact with allergens in this age group. There is an urgent need to perform appropriate studies to understand this disease as well as its prevalence and burden.

There were more epidemiologic studies reporting rhinitis in schoolchildren, but many do not include a diagnosis of allergy (skin tests and/or specific IgE), and so the differentiation between AR and nonallergic rhinitis cannot be made [49–51]. Other studies classify AR as seasonal or perennial, according to the occurrence of symptoms during the year and the type of allergen [52, 53]. However, this classification is not applicable in all countries. One cohort used the Allergic Rhinitis and its Impact

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**Table 4. Distribution of the studies included according to their methodology and variables**

<table>
<thead>
<tr>
<th>Methodology</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questionnaire-based study</td>
<td>153 (77.7)</td>
</tr>
<tr>
<td>References provided</td>
<td>61 (39.9)</td>
</tr>
</tbody>
</table>

**Atopy**

- tIgE: 93 (47.2)
- sIgE: 67 (34.0)
- Food allergens: 52 (77.6)
- Inhalant allergens: 49 (73.1)
- SPT: 126 (64.0)
- Food allergens: 68 (54.0)
- Inhalant allergens: 118 (93.7)
- Patch test: 8 (4.1)
- Maternal history of atopy: 135 (68.5)
- Paternal history of atopy: 130 (66.0)

**Lung function tests**

- Spirometry: 71 (36.1)
- Post-bronchodilator: 13 (18.3)
- Peak flow: 17 (8.6)
- BHR: 59 (30.0)
  - Eucapnic voluntary hyperventilation: 3 (5.1)
  - Exercise: 6 (10.2)
  - Histamine: 19 (32.2)
  - Hypertonic saline: 4 (6.8)
  - Methacholine: 23 (39.0)
  - Exercise + histamine: 1 (1.7)
  - Exercise + methacholine: 2 (3.4)
  - Hypertonic saline + methacholine: 1 (1.7)
- Biomarkers: 50 (25.4)
- Other tests: 47 (23.9)
- Disease severity: 68 (34.5)

**Sociodemographic variables**

- Ethnicity: 30 (15.2)
- Parental education: 35 (17.8)
- Socioeconomic status: 48 (24.4)
on Asthma (ARIA) classification and found that >50% of children with AR had persistent AR and were also more commonly sensitized to aeroallergens than those with mild persistent AR [54]. A cross-sectional study [34] compared the allergen-based classification of AR (seasonal vs. perennial) with the new ARIA classification, and found that they cannot be interchanged. Others have validated the modified ARIA severity classification to discriminate between a moderate and severe status [33].

**Eczema**

Many studies are devoted to the atopic march and the hygiene hypothesis to study the natural course of allergic diseases to find environmental determinants or disentangle disease heterogeneity (online suppl. Discussion). Most studies cannot be compared since they use different terms for defining atopic dermatitis/eczema. Two position papers [6, 55] suggested terms to standardize the terminology of this disease. In 2001, the use of ‘atopic eczema/dermatitis syndrome’ was suggested as an alternative term to ‘atopic eczema/dermatitis’ [55], and we found 1 study that used this term [56]. Later, in 2003, it was suggested that ‘atopic eczema/dermatitis syndrome’ be replaced with ‘eczema’, which could then be subclassified as ‘atopic eczema’ and ‘nonatopic eczema’ according to the presence or absence of IgE antibodies. We found a wide range of studies that use these terms, but also some that use ‘atopic dermatitis’ and ‘eczema’ interchangeably. In some countries, ‘atopic dermatitis’ is used, which is not consistent with the latest nomenclature [6]. There is an urgent need for an international definition of this disease to be established for reports in studies in the future.

**Urticaria**

We found 4 epidemiologic studies on childhood urticaria [57–59], mainly describing the acute and chronic forms [60]. More studies are needed.

**Anaphylaxis**

The literature on anaphylaxis is scarce and so there is a lack of information on its prevalence and characteristics in general, and in children in particular [61]. Only 1 study focused on anaphylaxis [62] and classified it according to the causative factor. However, a systematic review of validated methods to identify anaphylaxis reports 4 types, varying according to the trigger mechanism, i.e. IgE-mediated allergic (the most common, including food, medications and insect stings), IgE-independent allergic (formerly classified as anaphylactoid), nonallergic (uncommon, including physical factors and ethanol) and idiopathic [63].

**Food Allergy**

Allergic reactions to food can cause a large variety of symptoms including asthma, rhinitis, eczema, urticaria and anaphylaxis. Some food-allergic patients reported gastroenterological symptoms including nausea, stomach pain, vomiting or diarrhea. The best diagnostic procedure for food allergy is a double-blind, placebo-controlled, oral food challenge test [64]. Many recent studies have been reported by EuroPreVall using food challenges in the general population, but we have not reported these [30–32]. Conclusions about food allergy need to be revised by means of a new meta-analysis.

**Endophenotypes**

The elucidation of allergic phenotypes has been refined by including information on mechanisms, so-called ‘endophenotypes’ or ‘endotypes’ (a contraction of ‘endophenotypes’). Recently, a group of experts proposed that each endotype should form a distinct disease entity based on at least 5 of the 7 following parameters: clinical characteristics, biomarkers, lung physiology, genetics, histopathology, epidemiology and treatment response [65]. Around 25% of the studies included in our review examine some biomarkers. However, intensive efforts to classify asthma phenotypes according to their immunoprofiles have not yet led to a new classification of asthma in children [66]. The complexity of immune responses possibly needs to be addressed using systems biology rather than by a deterministic approach [66, 67]. Another approach is to use biomarkers in the definition of asthma endotypes [67–70]. Although these approaches have been rarely used for asthma [71], they are going to become an increasingly important feature of phenotyping [68].

**The Impact of the Findings**

The evidence gathered in this systematic review strongly supports the need for the standardization of phenotype definitions since characterization of disease phenotypes may significantly affect disease classification, and, therefore, any associations with potential determinants that may explain causal pathways. Moreover, disease phenotypes affect the choice of diagnostic tests, the sensitivity of disease prediction rules [72] and, most importantly, predict the responsiveness to therapeutic strategies [73].

Many phenotypes have so far been classified according to broad categories, i.e. based on one single dominant
characteristic up to several variables, risking an inherent bias which may ignore a potential overlap between groups. We therefore urge that international consensus on disease definitions and disease classification be reached. Much effort has been made to characterize diseases, but little or no effort has been made to validate them. With MeDALL, a consensus has been achieved for the definition of asthma, rhinitis and atopic dermatitis [12]. This could be used to define a common framework. Thus, future research on allergic phenotypes should focus on: (1) validation of phenotypes, (2) addressing multimorbidity and (3) disease severity, so as to add valuable knowledge about heterogeneity within phenotypes and the overlap across phenotypes. Recognizing the heterogeneous nature of allergic diseases should be a prerequisite for planning studies aimed at differentiating between different endo-/phenotypes and the sequential creation of robust, clinically relevant and endo-/phenotype-specific biomarkers and therapies to be able to target specific pathophysologies and include longitudinal outcomes [71].

In conclusion, the current literature on allergic diseases is characterized by great variations in classification, phenotypical entities and related terms. This reflects different approaches and research interests, but also the lack of a well-established methodological foundation for disease definitions and classifications. Surprisingly, so far, no systematic review has been reported in this field. Our study provides a detailed description of the large variety of allergic phenotypes and suggests future directions for research and standardization. It is important that better standards for the validation and replication of phenotypes be developed. To this end, international societies and current guidelines should make an effort to integrate the literature that is currently available.

Acknowledgements

This work was supported by MeDALL, a collaborative project conducted within the European Union under the Health Cooperation Work Programme of the 7th Framework Programme (grant agreement No. 261357). Mariona Pinart is a recipient of a 'Sara Borrell' postdoctoral contract (CD11/00090) from the Fondo de Investigaciones Sanitarias (FIS), Ministry of Economy and Competitiveness, Spain.

Disclosure Statement

There were no conflicts of interest.

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