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Systematic Review Protocol to Define Classical IgE-Associated Diseases from Birth to Adolescence: The MeDALL Study

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None

Additional Files:

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Additional file 1

Additional file 2

Additional file 3

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Abstract

BACKGROUND: Classical disease phenotypes are mainly based on descriptions of symptoms and the hypothesis that a given pattern of symptoms provides a diagnosis. With refined technologies there is growing evidence that disease expression in patients is much more diverse and subtypes need to be defined to allow a better targeted treatment.One of the aims of the Mechanisms of the Development of Allergy Project (MeDALL,FP7) is to re-define the classical phenotypes of IgE-associated allergic diseases from birth to adolescence,by consensus among experts using a systematic review of the literature and identify possible gaps in research for new disease markers.This paper describes the methods to be used for the systematic review of the classical IgE-associated phenotypes applicable in general to other systematic reviews also addressing phenotype definitions based on evidence.
METHODS/DESIGN: Eligible papers were identified by PubMed search (complete database through April 2011).This search yielded 12,043 citations.The review includes intervention studies (randomized and clinical controlled trials) and observational studies (cohort studies including birth cohorts, case-control studies) as well as case series.Systematic and non-systematic reviews,guidelines,position papers and editorials are not excluded but dealt with separately.Two independent reviewers in parallel conducted consecutive title and abstract filtering scans.For publications where title and abstract fulfilled the inclusion criteria the full text was assessed. In the final step, two independent reviewers abstracted data using a pre-designed data extraction form with disagreements resolved by discussion among investigators.
DISCUSSION: The systematic review protocol described here allows to generate broad,multi-phenotype reviews and consensus phenotype definitions.The in-depth analysis of the existing literature on the classification of IgE-associated allergic diseases through such a systematic review will 1) provide relevant information on the current epidemiologic definitions of allergic diseases,2) address heterogeneity and interrelationships and 3) identify gaps in knowledge.

Background

Allergic diseases are extremely common and patients frequently suffer from IgE-mediated reactions [1]. Up to 50% of the population in certain age groups and countries are sensitized to allergens. Major IgE-associated chronic diseases include rhinitis (and conjunctivitis) [2], asthma [3], atopic dermatitis [4], food allergy [5] that may express a variety of symptoms including anaphylaxis if the expression of acute severe symptoms is generalized in different organs.

The overarching aim of the EU FP7-funded project MeDALL (Mechanisms of the Development of Allergy) is to generate novel knowledge on the origins of the epidemic of IgE-associated allergic diseases in children [6]. Its main objective is to understand the mechanisms underlying the complex relations between environmental, genetic and socio-economic factors influencing the initiation of allergy. One novel characteristic of MeDALL is to include a two-step approach comparing the classical phenotypes, which are hypothesis-driven and defined by experts, and novel phenotypes which are established by using unsupervised statistical methods [7].

MeDALL Work Package 2 (WP2) aims at re-defining the phenotypes of IgE-associated allergic diseases in children by classical approaches using interactions between subsequent expert meetings and a systematic review of the literature. This is carried out in a stepwise manner: the first step consisted of an expert meeting held in Barcelona on June 29-30, 2011 (http://www.medall-fp7.eu) to agree on the working definitions of IgE-associated diseases. The second

step is to review the literature on the phenotypes and course (from infancy to adolescence) of diseases. The systematic review protocol developed to this end will help experts to improve the hypothesis-driven definitions of other complex phenotypes. The methodology for the systematic review and the disease definitions as agreed by the MeDALL experts are presented in this paper.

Rationale for the review protocol of the literature on classical phenotypes

Unlike most systematic reviews, the present one addresses a complex ill-defined question applied to a wide range of very common and often overlapping phenotypes usually considered as independent entities.Thus, tens of thousands of documents may be considered eligible and clear-cut screening criteria were difficult to establish, leading to the development of an interative, multi-step review protocol.

The topics of the systematic review include as relevant topics 1) definitions of classical allergic diseases, 2) information about their heterogeneity and 3) interrelationships from birth to adolescence. The aim of the literature review on the classical phenotypes is to systematically describe the clinical and/or population-based phenotypes of IgE-associated diseases or conditions (Illustration 1). The description of the classical phenotypes resulting from the systematic review and the MeDALL expert meeting will then serve as the basis for comparison with the novel statistically unsupervised phenotypes and their omics assessments in MeDALL cohorts [6].

In the protocol of this systematic review of classical phenotypes, we have included both organ related diseases (lungs, nose, eyes, skin, and generalized allergy) and reactions after exposure to an allergen (e.g. food allergy). Food allergy was considered separately since symptoms are very broad and may include reactions to all organs and systems.

Review objectives

What do we understand by “phenotype”? In MeDALL an allergic phenotype corresponds to the clinical expression of diseases or conditions including one or more of the following characteristics: family history, signs, symptoms, pulmonary function tests (PFT),serum specific-IgE and skin prick tests (SPT).

Primary objective: To identify clinically expressed, population-based, phenotypes of IgE-associated diseases or conditions listed in Illustration 1 and their interrelationships across phenotypes, from 0-18 years in order to redefine classical IgE-associated phenotypes.

Secondary objectives:

a) To explore temporal heterogeneity within phenotypes.

b) To appraise the various methodological approaches used to measure phenotypes.Approaches refer to study design and types of measures (e.g. specific IgE levels, SPT, PFT, co-morbidities, questionnaires).Depending on the data used, distinct phenotypes can be defined.

Methods/Design

Type of studies and participants:

The systematic review is mainly focused on original articles.The list of inclusion and exclusion criteria is provided in Illustration 2.

Dealing with lack of information

If after examining the full-text report the study does not provide enough information to ascertain suitability for inclusion and is classified as “unclear”, authors of the studies will be contacted.In case of failure to communicate with the primary investigators, or if there is no response within two weeks, we will list the particular study as “potentially relevant study”.

Dealing with duplication

Duplication can occur because there are duplicated manuscripts, translated reports or follow-up studies with the same population describing different numbers of participants and/or outcomes.Because these publications can introduce substantial biases, we will extract data from all reports directly into a single data collection treating them as a single study.

Reporting study selection:

A flow chart describes the study selection process according to the PRISMA Statement diagram [8] [see Additional file 1].

MeDALL process of re-defining classical phenotypes of IgE-associated diseases

In MeDALL, a six step process was established for the systematic review to re-define classical phenotypes of IgE-associated diseases.

1. Establishment of the list of phenotypes by expert consensus.

2. Review of international guidelines and consensus documents (Illustration 3) on the phenotypes listed in Illustration 1 to develop working questions.

3. Development of working definitions for a consensus expert meeting.

4. Development of a questionnaire for the identification of the classical phenotypes in the historical birth cohorts participating in MeDALL [7].

5. Development of discussion materials for the expert meeting.

6. Systematic review of the literature concerning the classical phenotypes.

Based on a consensus document (the MeDALL

proposal [6]) and the MeDALL scientific conference (http://www.medall-fp7.eu), an initial list of phenotypes was identified for review (listed in Illustration 1). From the recent guidelines and consensus reports two MeDALL experts (J. Bousquet and J. M. Antó, MeDALL website: http://www.medall-fp7.eu) prepared working definitions of the included phenotypes for discussion. These definitions [see Additional file 2] were sent to the expert panel for initial discussion prior to the meeting.For each of the included phenotypes the questionnaire included the questions and wording to be used for the identification of the classical phenotypes in the participating cohorts. For each of the defined phenotypes proposed in step 3, a review paper was written by JMA and JB (http://www.medall-fp7.eu) to be the basis for the expert meeting. The discussion papers were distributed prior to the expert meeting [see Additional file 2]. The working definitions of the IgE-associated allergic phenotypes agreed by MeDALL experts after reviewing the documents presented during the meeting are summarized in the Additional file 3. Hereunder we describe the stages that were carried out for the on-going systematic review.

Systematic review of the literature concerning the classical phenotypes

The systematic review was reported in accordance with the statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement) [8, 9].In order to deal with a large number of potentially eligible documents a four-step approach was followed (Illustration 4).The literature was searched using computerized bibliographic databases such as MEDLINE through the PubMed webpage (http://www.ncbi.nlm.nih.gov/pubmed/), which consisted of several stages using the knowledge management software system of Biomax (MeDALL partner 16).

Stage 1: Search strategy. Potentially eligible papers were identified by a classical MEDLINE search using PubMed (complete database through April 2011) with the working definitions.The search terms used were Asthma [tiab] OR respiratory sound*[tiab] OR wheez*[tiab] OR rhinitis[tiab] OR rhinoconjunctivitis[tiab] OR food allergy[tiab] OR food hypersensitivity[tiab] OR atopic dermatit*[tiab] OR eczem*[tiab] OR anaphyla*[tiab] OR urticaria[tiab] OR allerg*[tiab] AND (phenotyp*[tiab] OR IgE[tiab] OR immunoglobulin E[tiab] OR skin prick[tiab] OR atopic*[tiab] OR atopy[tiab]). Search terms were identified from expert knowledge and curated from literature mining from collected high-frequency terms in allergy related publications.

The literature mining derived high-frequency terms showed good accordance with the expert derived key search terms.This result is not self-evident as in general high-frequency terms co-occurring with expert defined terms can provide significant, relevant extensions of the publications covered by the mining process.In this case the good accordance provided important independent evidence for the completeness of the expert defined key search terms and therefore the high sensitivity of the search. Key search terms added as result of the literature mining were “respiratory sound”, “food allergy” and “food hypersensitivity”, “atopic dermatit*” and “anaphyla*”.

The search terms retrieved about 49,000 publications from PubMed which were filtered for publications relevant to the definition of childhood allergy phenotypes by setting appropriate constraints. The constraints concerned PubMed provided manually curated keywords and MeSH terms such as “child”, “children”, “infant” or “adolescent” as well as the use of other Boolean operators resulting in 12,043 citations (Illustration 4).We restricted the search to English language publications.

Stage 2: Screening of titles. The 12,043 identified publications were manually filtered for relevance based on their titles. Two independent reviewers conducted title scans in a parallel fashion. The title review stage was designed to capture the maximum number of studies reporting on the hypothesis-driven identification of IgE-associated phenotypes, phenotype heterogeneity or overlap across phenotypes. To ensure that the two reviewers had a similar understanding of inclusion and exclusion criteria, the first 400 titles were screened and scored as “included” or “excluded” followed by a consensus discussion between the reviewers in order to reach agreement on the interpretation of the criteria. Discrepancies were solved by consensus after screening the abstracts. To ascertain the number or percentage of articles that could be missed by screening the title only, a sensitivity analysis was performed. The same two reviewers screened the first 600 abstracts that were previously excluded from the list of 12,043 titles by means of a table of random numbers, and only two abstracts were found to be clearly eligible for inclusion. Hence, it was concluded that one of the methodological limitations of this systematic review is that around 40 studies of a total of 12,043 citations (0.003%) rated as excluded would have been included if we had screened the abstracts. This step resulted in 985 titles considered as potentially eligible, which were promoted to the abstract review stage.

Stage 3: Screening of abstracts. The 985 abstracts selected in step 2 were reviewed by a panel. Prior to the panel screening of abstracts a pilot test to assess

abstract screening validity was conducted in order to ensure that all reviewers understood the protocol, the objectives of the protocol as well as the defined inclusion and exclusion criteria. The pilot test was also conducted so that all reviewers participating in the systematic review could have the opportunity to raise questions regarding the readability of the protocol and also with the aim to improve the pre-designed review form if necessary. 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 through meetings or telephone calls, all reviewers were confident enough to score the abstracts.

Criteria for inclusion (Illustration 5) were studies conducted in subjects aged 0 to 18 years, which primary objectives were:

• To identify clinically expressed, population-based phenotypes of IgE-associated diseases or conditions including asthma/wheezing, atopic eczema, rhinoconjuctivitis, food allergy, urticaria and anaphylaxis, as well as their interrelationships;

• To explore heterogeneity within disease entities or phenotypes;

• To evaluate or validate methods or measurements for the diagnosis of IgE-associated diseases. Abstracts were categorized as “included for full text”, “excluded for full text” and “unclear”.

All abstracts were reviewed by two reviewers independently. When two reviewers considered the abstract eligible for inclusion or one reviewer scored the abstract as “included” and the other as “unclear”, the study was retrieved for full text assessment. Conversely when the two reviewers considered an abstract to be “excluded”, the full text was not retrieved. Disagreements were resolved through referral to a third reviewer.

Stage 4: Data abstraction of full text. A panel reviewed full texts of all selected publications resulting from stage 3 and identified those that were eligible according to the same criteria as stated in step 3. A pre-designed data extraction form has been now developed and data from the texts in full will be abstracted by two reviewers independently with disagreements resolved by discussion among investigators.

To provide a technological platform for the systematic review the BioXM environment was used. It is a generic framework for the dynamic, graphic generation of domain specific knowledge representation models based on specific objects and their relations supporting annotations and ontologies [10]. It was configured to provide the document and process management functions (e.g. status overviews, quality checks) and user interfaces (e.g. task assignments, input forms) for the staging of literature and the multi-referee review as described below. Its literature mining functions [11] were applied to generate completeness estimates for the search terms (Stage 1) and initial filtering criteria (Stage 2).

Discussion

The systematic review of IgE-associated diseases follows a detailed protocol, presented here, with strict and precise steps to define classical phenotypes as proposed by MeDALL experts.This is the first attempt to generate a definition of IgE-associated phenotypes based on a systematic review and we believe the developed protocol is highly valuable and applicable to systematic reviews for other complex and convoluted phenotypes.

Limitations

There are however some limitations to be considered.If we compare the structure of the search strategy of a Cochrane review (http://www.cochrane-handbook.org/) we will see that it is mainly focused on the conduct of tailored search strategies for each of the following databases: The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE plus additional hand searching. Moreover, they strongly recommend avoiding too many different search concepts although a wide variety of search terms should be combined with OR within each concept. Cochrane reviews encourage the performance of high sensitive searches but at the same time recognise that depending on the review question it may be necessary to strike a balance between sensitivity and precision. This systematic review addresses a complex question applied to several entities that are currently dealt with separately but that often overlap.Thus, the iterative process of the search strategy is not very specific yielding a huge number of documents that has the potential to be considered eligible.The large number of excluded articles illustrates the difficulty of performing a specific literature search on such a broad question and the lack of well-established disease classification in the literature. In addition, an important aspect of this review is its role in assisting an expert panel within a tightly scheduled sequential approach. Consequently, the search strategy was conducted in a way that specificity concerning the primary question was prioritized against sensitivity. In addition we only

included studies written in English, and we have also limited the search to few wide repository databases such as MEDLINE through the PubMed webpage. Nonetheless, to check for completeness of the bibliographic database an identical literature search will be executed in EMBASE and results will be compared to those obtained by MEDLINE. Furthermore, relevant review articles and original articles will be retrieved and their reference lists will be searched for additional articles. According to the expert panel, some studies may be missed due to the language restriction.However, it was thought to be quite unlikely to have missed studies that could provide added value to the classical definitions of the different IgE-associated phenotypes. Reviews most frequently included clinical definitions currently used for purpose of disease management. However, confusion may occur in verbal and written discourse among physicians because of lack of agreement on how diseases should be defined; especially when the aetiology of the disease is not fully understood and phenotypes may vary over time [12].In addition, clinical and epidemiological interpretations of these definitions may differ as they often serve different purposes. Furthermore, the application of definitions involving retrospective information (like “early transient wheezing”) may not be useful for clinical management as they depend on age.In other words, one very important limitation is the lack of a gold standard to validate the definitions.

Strengths

The present MeDALL protocol describes a comprehensive and expert-based systematic review on major IgE-associated allergic phenotypes.We have not yet found a review or a systematic review assessing in an integrative way all allergic diseases considered here.In contrast, we have found a great body of non-systematic reviews assessing phenotypes of one single entity such as asthma [13] and rhinitis [14]. Performance, analysis and interpretation of our systematic review will be supported by an international, multidisciplinary global consensus panel of experts in allergic diseases and related fields.

In MeDALL two approaches to define disease phenotypes are considered: the classical and the novel approach.Here in this paper we have only reviewed the classical approach, considering that a systematic literature review is the best approach to gather sufficient evidence to better define classical allergic phenotypes, the heterogeneity of the different allergic diseases and their interrelationships.Re-defining IgE-associated allergic diseases with the coordinated effort of a systematic review of the literature, literature mining, consensus among experts and comparison with hypothesis-free phenotypes (novel phenotypes) will improve the daily clinical practice when treating patients with very heterogeneous syndromes, because it will facilitate the identification of more homogeneous subgroups of patients that can have individualized diagnostics and receive personalized treatments.

The definition of classical phenotypes using a systematic review will provide relevant information:

• To build a common database with an inventory of the studies and cohorts (e.g. MAS [15], GINI [16], PARIS, [17], Tucson [18], BAMSE [19], ALSPAC and PIAMA [20]) that have contributed to the identification of the classical phenotypes.

• To address the methods that researchers have used for the classification or description of phenotypes such as the study design, type of study, etc.

• To analyze the temporal evolution of the classification of the disease entities in terms of labels and description of the diseases.

• To investigate interrelationships among phenotypes and provide hypotheses for future quantitative meta-analysis.

• To provide the basis for future cohorts using better standardized definitions of phenotypes and sub phenotypes.

• To identify gaps of existing markers allowing more targeted approaches for future research

Importance of phenotype definitions:

A “phenotype” is defined as the expression of physical traits determined by genetic makeup and environmental influences [21]. This concept translated into epidemiology considers phenotypes as hypothesis-based disease entities that can be aetiologically distinguishable from other conditions or syndromes affecting a group of patients [13].Thus, a phenotype can be considered as a cluster of either clinical or pathological features or both, which are likely to be associated [22]. Current classification of phenotypes is based mainly on etiologic factors or clinical characteristics of the disease [13] such as symptom patterns, which depend on the age, gender, genetic background, and environmental factors. In the original protocol, we defined “allergic phenotype” as the clinical expression of diseases including a minimum of one of the following characteristics: family history, signs, symptoms, PFT, serum specific-IgE and SPTs. Since there is no uniform definition for allergic phenotype it was considered useful to evaluate pulmonary function tests, BHR, and measures of atopy such as IgE and skin-test reactivity to common

allergens. However, during the expert meeting held last summer in Barcelona, many experts thought that family history, which is a risk factor, is difficult to use as a clinical characteristic of a child's phenotype because the majority of children that have developed allergy during the first years of life are born into families with no history of atopy. Phenotypes should have real predictive value since individuals clustering within a particular phenotype should also exhibit a similar treatment response profile due to sharing specific pathophysiologic abnormalities [23].

In other diseases such as Chronic Obstructive Pulmonary Disease (COPD), attempts have been made to re-define the classic definition of the disease e.g. [24, 25], one identified and validated three different COPD phenotypes by means of unsupervised methods [24], and the second identified a frequent-exacerbation phenotype that is independent of disease severity [25]. In both cases, the new classification was related to the evolution of the disease [24, 25].The ultimate goal of phenotyping is to enable clinicians and researchers to identify groups with unique prognostic or therapeutic characteristics. IgE-associated diseases are heterogeneous and the overlaps between them are unclear.Hitherto, it is not yet clear whether all different disease subtypes represent the variable expression of one single disease or whether some of the disease subtypes represent distinct diseases with similar symptomatology [26]. There is a pressing need to develop a precise definition of phenotypes to gain new insights about the aetiology of the disease, the underlying genetic basis for the disease, treatment response and/or management strategy and prognosis. Because the underlying biologic and physiologic mechanisms of asthma are still not yet fully understood, phenotypes have an undisputed standing in the research on childhood asthma, and their existence is often uncritically accepted [13], making the interpretation of the literature and the agreement among experts more complex and occasionally confusing.

Other systematic reviews on disease definitions:

Hundreds of reviews have focused on the classification of allergic diseases into phenotypes. However, the MeDALL review is the first one to our knowledge to be conducted in a systematic fashion in allergy.Few systematic reviews dealing with classification of heterogeneous syndromes have been published between 2005 and 2011 in rheumatology [27], psychiatry [28, 29], endocrinology [30], chronic health conditions [31], sports medicine [32], hematology [33], and neurology [34]. Most systematic reviews selected original research articles except three of them that also included review articles, guidelines and/or editorials [27, 32, 33]. Two systematic reviews selected the studies regardless of the language of publication [27, 30] and one did not specify any language restriction [29]. All of them carried out a systematic literature search throughout several databases, except two systematic reviews [27, 33] that searched the MEDLINE database only. Additional articles were identified through a comprehensive manual search of the references of retrieved articles. Most of these reviews highlight the need of a gnosologic classification of a disease especially when the disease under study is heterogeneous and there is a lack of standardization in diagnosis and management, wide discrepancies in operative terminology and lack of standardized classification, which could be based on international consensus statements.

Conclusions:

We believe that the design of this protocol will facilitate the retrieval of relevant papers, the assessment of the quality of included studies, and the systematic evidence-based description of the clinical and/or population-based phenotypes of IgE-associated diseases or conditions. The in-depth analysis of the existing literature on the classification of IgE-associated allergic diseases through a systematic review will 1) provide relevant information on the current epidemiologic definitions of allergic diseases, 2) address heterogeneity and interrelationships of clinical presentations, 3) identify gaps in knowledge and 4) serve as the basis for redefinition of classical IgE associated phenotypes for future studies in MeDALL.

Abbreviations

AAD: American Academy of Dermatology

ABAP: Aktionsbündnis Allergiepräven-tion (German Network on Allergy Prevention)

ARIA: Allergic Rhinitis and its Impact on Asthma

ASCIA: Australasian Society of Clinical Immunology and Allergy Anaphylaxis Working Party

BP: Blood Pressure

BSACI: British Society for Allergy and Clinical Immunology

BTS/SIGN: British Thoracic Society/ Scottish Intercollegiate Guidelines Network

COPD: Chronic Obstructive Pulmonary Disease

DBPCFC: Double-blind Placebo-Controlled Food Challenge

EADV: European Academy of Dermatology and Venereology

EPR: Expert Panel Report

EU: European Union
FP7: Framework Programme 7
GINA: Global Initiative for Asthma
IgE: Immunoglobulin E
ISAAC: International Study of Asthma and Allergies in Childhood
MeDALL: Mechanisms of the Development of Allergy
NACI: National Advisory Committee on Immunisation
NHLBI: National Heart, Lung, and Blood Institute
NIAID: National Institute of Allergy and Allergic Diseases
NICE: National Institute for Health and Clinical Excellence
NIH: National Institutes of Health
PEF: Peak Expiratory Flow
PFT: Pulmonary Function Tests
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SPT: Skin Prick Test
WAO: World of Allergy Organisation
WP2: Work Package 2

Competing interests

MW declares that he has received grant support from Thermo Fischer.MW is a member of advisory boards and has given paid lectures for Airsonett, ALK-Abello, GSK, MSD, Novartis and Thermo Fischer.DM is employed at a commercial organization, Biomax Informatics AG, and will therefore be affected by any effect of this publication on the commercial version of the BioXM knowledge management and BioLT literature mining software. TZ is consulting with the following companies: Ansell, Bayer Schering, Fujisawa, HAL, Henkel, Kryolan, Leti, MSD, Novartis Pharma GmbH, Procter and Gamble, Sanofi-Aventis, Schering Plough, Stallergenes, UCB. TZ is also affiliated with the following organizations: the Scientific Advisory Board, German Society for Allergy and Clinical Immunology Expert Commission "Novel Food" of the German Federal Ministry of Consumer Protection Head, European Centre for Allergy Research Foundation (ECARF) Committee member, WHO-Initiative Allergic Rhinitis and its Impact on Asthma (ARIA) Member, World Allergy Organization Communications Council Member of the WAO Special Committee on Allergy Diagnosis and Molecular Allergology Secretary General,Global Allergy and Asthma European Network (GA²LEN). The other authors declare that they have no competing interests.

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Illustrations

Illustration 1

IgE-associated phenotypes considered in the systematic review

IgE associated phenotypes considered in the systematic review

Rhinitis/rhinoconjuctivitis or allergic rhinitis (AR)
Eczema/ Atopic dermatitis (AD)
Asthma or wheezing
Food allergy (FA)
Anaphylaxis

Urticaria

Illustration 2

Inclusion and exclusion criteria for the systematic review

Inclusion and exclusion criteria for the systematic review

Included studies:
Studies whose primary aim is to define, characterize or compare different phenotypes, or to explore the heterogeneity of the different allergic diseases; or to explore their interrelationships. The study population only includes subjects aged 0 to 18 years. These include original papers of:

- Cross-sectional studies
- Case-control studies
- Case-series
- Prospective and retrospective longitudinal observational studies including (birth) cohorts and case-control studies
- Intervention studies (randomized and clinical controlled trials)

Excluded studies:

- Studies whose primary aim is to assess mechanisms of phenotypes and/or the aetiology of the phenotypes (i.e. omic studies)
- Studies that do not provide at least one of the following direct and relevant information about phenotype validation, heterogeneity within phenotypes or the interrelationships between phenotypes (overlap and comparability).
- Studies using unsupervised statistical methods (e.g. any type of cluster, latent class analysis).
- Studies including subjects aged over 18 years and studies including both children and adults if results are not presented separately for those younger than 19 years.
- Case reports.
- Ecological studies.
- Experimental studies involving either animals or cell culture or both.
- Narrative reviews.
- Editorials.

Guidelines, position papers or statements in which the evidence for phenotype definition is not developed.

Illustration 3

Guidelines used to develop questions

Guidelines used to develop questions

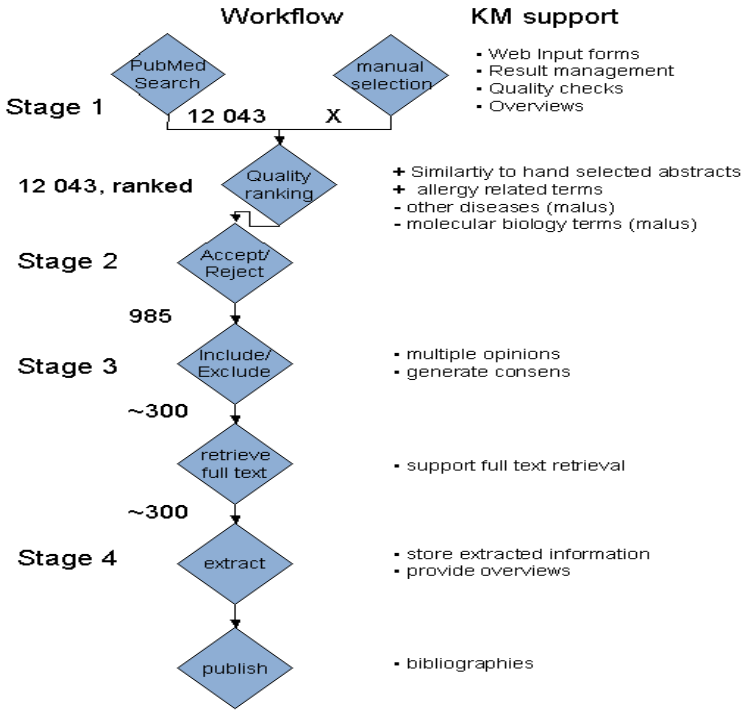
- Asthma or wheezing: BTS/SIGN (British Thoracic Society/ Scottish Intercollegiate Guidelines Network [35][35], GINA (Global initiative for Asthma [36], NHLBI-EPR3 (National Heart, blood and Lung Institute-Expert Panel Report 3 [37]
- Atopic eczema: NICE (National Institute for Health and Clinical Excellence [38], AAD (American Academy of Dermatology [39], ABAP [40], EADV (European Academy of Dermatology and Venerology [41]
- Food allergy: NIAID (National Institute of Allergy and Infectious Diseases) [42], ASCIA (Australasian Society of Clinical Immunology and Allergy [43]
- Rhinitis or rhino-conjunctivitis: ARIA (Allergic Rhinitis and its Impact on Asthma) [2]

Anaphylaxis: NACI (national Advisory Committee) [44]

Illustration 4

The four steps of the literature review. Stage 1: Search strategy. Potentially eligible papers were identified by MEDLINE search using PubMed. Stage 2: Screening of titles. Two independent reviewers conducted title scans in a parallel fashion. Stage 3: Screening of abstracts. The 985 abstracts selected in step 2 were reviewed by a panel. Stage 4: Data abstraction of full text. Data will be abstracted using a pre-designed data extraction form by two reviewers independently.

The four steps of the literature review.

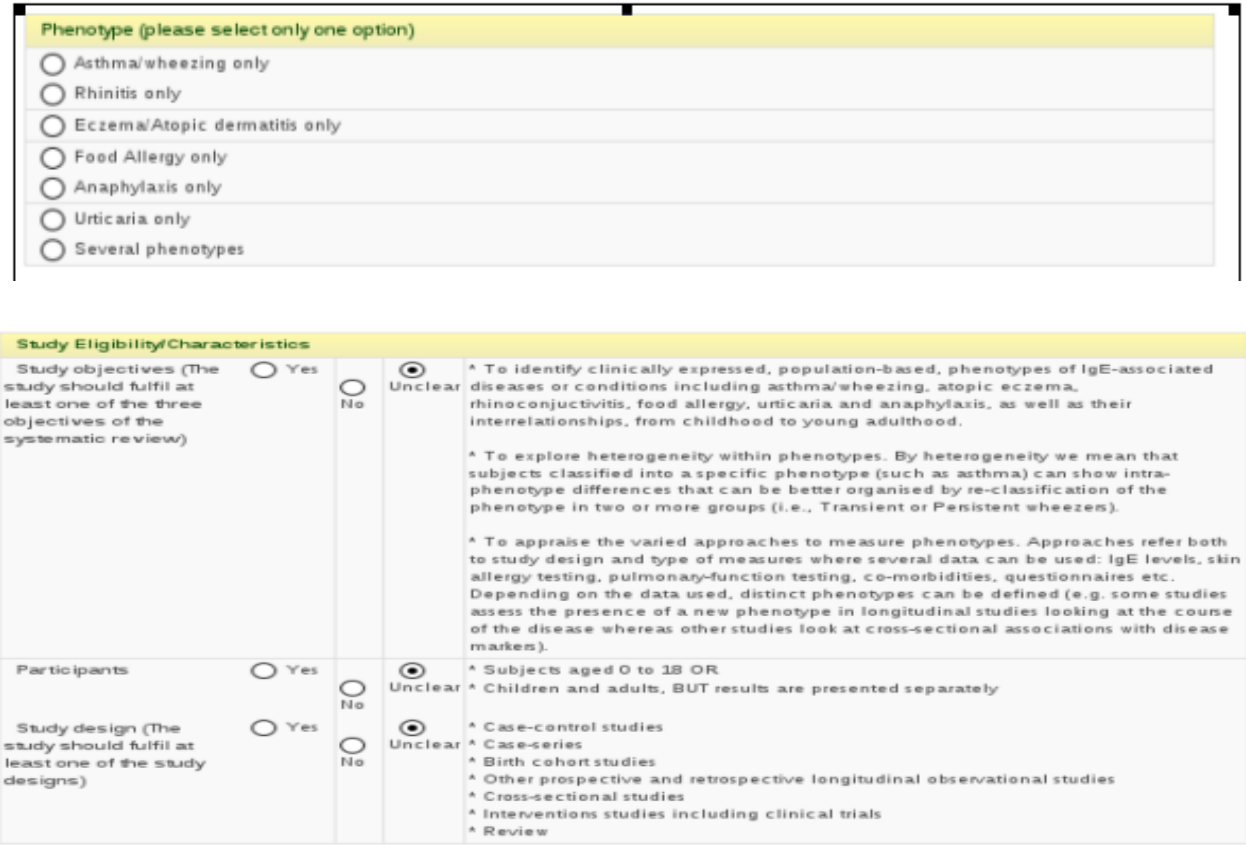


The four steps of the literature review. Stage 1: Search strategy. Potentially eligible papers were identified by a classical MEDLINE search using PubMed resulting in 12,043 citations. Stage 2: Screening of titles. Two independent reviewers conducted title scans in a parallel fashion. Stage 3: Screening of abstracts. The 985 abstracts selected in step 2 were reviewed by a panel. Stage 4: Data abstraction of full text. Data will be abstracted using a pre-designed data extraction form by two reviewers independently with disagreements resolved by discussion among investigators.

Illustration 5

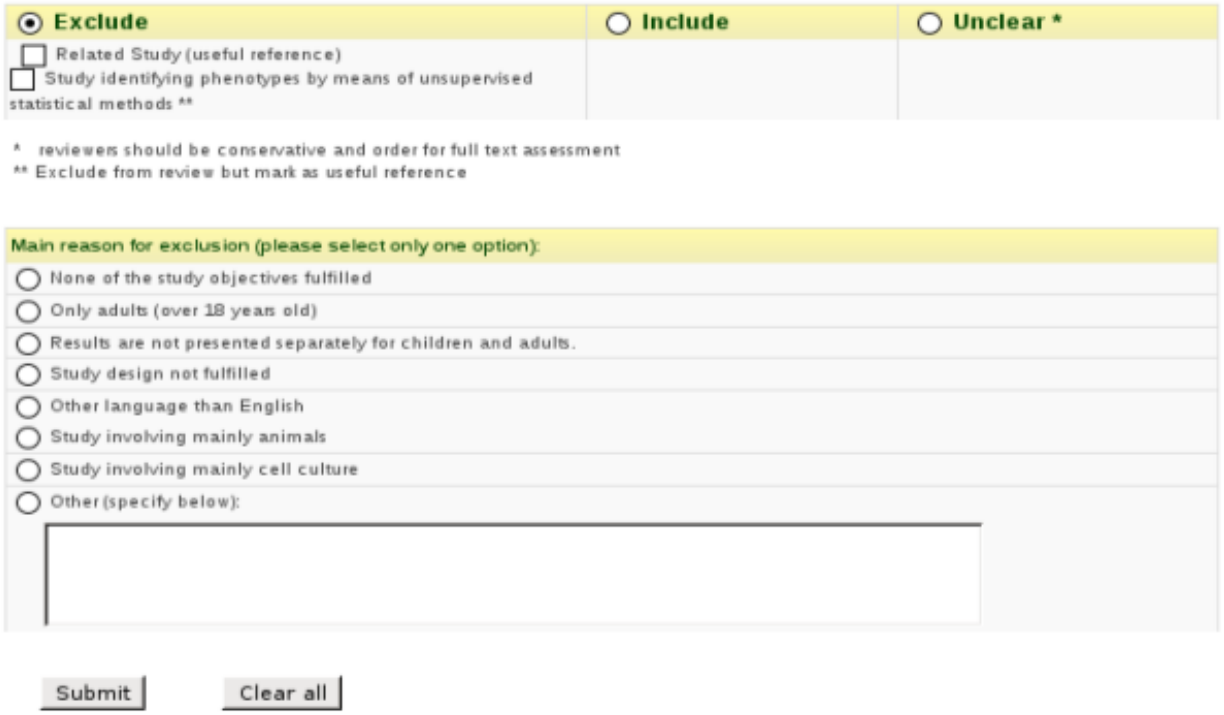
The Stage 3 review input form. Two reviewers screened all abstracts independently, filled in an abstract scoring form and classified them as included, excluded or unclear.

The Stage 3 review input form.



Phenotype (please select only one option)
◯ Asthma/wheezing only
◯ Rhinitis only
◯ Eczema/Atopic dermatitis only
◯ Food Allergy only
◯ Anaphylaxis only
◯ Urticaria only
◯ Several phenotypes

Study Eligibility/Characteristics				
Study objectives (The study should fulfil at least one of the three objectives of the systematic review)	◯ Yes	◯ No	◉ Unclear	* To identify clinically expressed, population-based, phenotypes of IgE-associated diseases or conditions including asthma/wheezing, atopic eczema, rhinoconjuctivitis, food allergy, urticaria and anaphylaxis, as well as their interrelationships, from childhood to young adulthood. * To explore heterogeneity within phenotypes. By heterogeneity we mean that subjects classified into a specific phenotype (such as asthma) can show intra-phenotype differences that can be better organised by re-classification of the phenotype in two or more groups (i.e., Transient or Persistent wheezers). * To appraise the varied approaches to measure phenotypes. Approaches refer both to study design and type of measures where several data can be used: IgE levels, skin allergy testing, pulmonary-function testing, co-morbidities, questionnaires etc. Depending on the data used, distinct phenotypes can be defined (e.g. some studies assess the presence of a new phenotype in longitudinal studies looking at the course of the disease whereas other studies look at cross-sectional associations with disease markes).
Participants	◯ Yes	◯ No	◉ Unclear	* Subjects aged 0 to 18 OR * Children and adults, BUT results are presented separately
Study design (The study should fulfil at least one of the study designs)	◯ Yes	◯ No	◉ Unclear	* Case-control studies * Case-series * Birth cohort studies * Other prospective and retrospective longitudinal observational studies * Cross-sectional studies * Interventions studies including clinical trials * Review



The Stage 3 review input form. Two reviewers screened all abstracts independently, filled in an abstract scoring form and classified them as included, excluded or unclear.

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