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Birth cohorts in asthma and allergic diseases: Report of a NIAID, NHLBI, MeDALL joint workshop

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Abstract

Population-based birth cohorts on asthma and allergies increasingly provide new insights into the development and natural history of the diseases. Over 130 birth cohorts focusing on asthma and allergy have been initiated in the last 30 years. A NIAID (National Institute of Allergy and Infectious Diseases), NHLBI (National Heart Lung and Blood Institute), MeDALL (Mechanisms of the Development of Allergy, Framework Programme 7 of the European Commission) joint

workshop was held in Bethesda, MD, USA September 11–12, 2012 with 3 objectives (1) documenting the knowledge that asthma/allergy birth cohorts have provided, (2) identifying the knowledge gaps and inconsistencies and (3) developing strategies for moving forward, including potential new study designs and the harmonization of existing asthma birth cohort data. The meeting was organized around the presentations of 5 distinct workgroups: (1) clinical phenotypes, (2) risk factors, (3) immune development of asthma and allergy, (4) pulmonary development and (5) harmonization of existing birth cohorts. This manuscript presents the workgroup reports and provides web links (AsthmaBirthCohorts.niaid.nih.gov or www.medall-fp7.eu) where the reader will find tables describing the characteristics of the birth cohorts included in this report, type of data collected at differing ages, and a selected bibliography provided by the participating birth cohorts.

Keywords

Allergy; asthma; birth cohorts; NHLBI; NIAID; MeDALL

Introduction

Asthma and allergic diseases commonly appear during infancy and tend to persist until adult life, thus birth cohort studies help to understand their determinants and evolution. Over 130 birth cohorts focusing on asthma and allergy have been initiated in the last 30 years [1,2,3] and some have followed the participants for over 30 years.[4,5]

Work has begun to pool information across birth cohorts.[3] To further improve our understanding of existing asthma birth cohorts, an Asthma Birth Cohort Workshop was held in Bethesda, MD, USA on September 11–12, 2012. The meeting was jointly sponsored by the National Institute of Allergy and Infectious Disease (NIAID), and the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH), and MeDALL (Mechanisms of the Development of Allergy, FP7, European Commission). The workshop allowed epidemiological, clinical and laboratory researchers conducting research on asthma and other allergic diseases in birth cohorts, to meet to address a wide research agenda. Representatives from major birth cohorts on asthma and allergies from North America, Europe, Asia, and Australasia attended.

The workshop had the objectives of (1) documenting the knowledge that asthma/allergy birth cohorts have provided, (2) identifying the knowledge gaps and inconsistencies and (3) developing strategies for moving forward, including potential new study designs and the harmonization of existing birth cohort data.

The meeting was organized around the presentations of 5 distinct workgroups, 4 of which were charged with reviewing available birth cohort data and preparing a presentation of results and knowledge gaps in pre-identified topics—asthma phenotypes, risk factors, immune development, pulmonary development, while the 5th workgroup worked to identify approaches for data pooling and harmonization (Table 1). Before the meeting, investigators from birth cohorts in North America, Europe, Asia and Australasia were sent a questionnaire to report their findings to date relevant to the workgroups (Table 2). The workgroups used

this information along with extant literature and expertise as the basis for their reports. The draft reports were presented and discussed at the meeting.

This article contains the final reports incorporating the input obtained from the meeting attendees. Additional information gathered as part of the workshop is available at the NIAID website (AsthmaBirthCohorts.niaid.nih.gov) and MeDALL website (www.medall-fp7.eu). At these sites, the reader will find the characteristics of the birth cohorts included in this report, types of data collected at differing ages, and a selected bibliography provided by the participating birth cohorts. The database allows the user to search for data collected across cohorts. The database will be updated as more cohorts are identified.

Workgroup 1: Clinical Phenotypes (group membership: Table 1)

Current definition and classification of childhood wheezing/asthma and allergic diseases

Birth cohort studies have been a highly productive source of knowledge about the characteristics of asthma phenotypes in childhood because of their unique longitudinal nature.

Studies in asthma have often used definitions developed by ISAAC[6] and partly adopted by European birth cohort collaborations GA^{2}LEN[7] and MeDALL[8,9], in particular "physician diagnosed asthma." In some studies, definitions have combined symptoms and markers such as lung function and airway hyper-responsiveness (AHR) to improve their validity.[10] Commonly, symptoms were combined with IgE measurement to stratify allergic and non-allergic subjects. Other approaches have included health care data using record linkage and response to treatment (inhaled steroids) as a diagnostic criterion. Few cohorts have studied asthma severity or other specific phenotypes like exercise induced-asthma, cough and difficulty breathing. Most longitudinal studies in asthma have adopted the wheezing phenotypes definitions described in the Tucson birth cohort (USA).[11] The etiological classification of wheezing (episodic viral wheeze and multi-trigger wheeze[12]) has been less often used. An alternative approach has used scoring systems like the Asthma Predictive Index[13] or qualitative categories (like definite, probable, and possible asthma).

For rhinitis, the term "allergic" is restricted to symptoms with demonstrable IgE sensitization (skin tests and/or serum specific IgE). The term atopic dermatitis or atopic eczema is reported in the majority of birth cohorts but definitions vary.

Unsupervised statistical techniques like latent class or cluster analyses were used to identify and define asthma phenotypes.[8,9,14] Using latent class analysis in ALSPAC (UK) and PIAMA (NL), wheezing patterns were in agreement with the Tucson classification.[11,15,16] MAAS (UK) used another unsupervised approach to describe multiple longitudinal patterns of sensitization.[17] This is an area of growing interest and many cohorts are part of MeDALL,[8,9] which is applying both hypothesis-driven and data-driven (unsupervised techniques) to redefine the asthma and allergic phenotypes.[9]

The contribution of birth cohort studies to understand asthma and allergy phenotypes

In the Tucson birth cohort, late onset and persistent wheezing, together with AHR and low airway function during childhood, are predictors of new asthma in young adulthood.[18] Reduced lung function at birth is associated with an increased risk of asthma by the age of 10 years and with a low respiratory function at the age of 22.[19,20] Lung function patterns have been studied in PIAF (Australia) but the lung function impairment in children with transient wheeze was not replicated.[21]

MAS (Germany) failed to show that exposure to inhaled allergens was a causal determinant of asthma[22], a finding confirmed by other studies. However, in MAS, sensitization to inhaled allergens and persistence of sensitization during childhood was associated with persistence of wheezing at school age.[23] MAS showed that children with non-allergic wheezing are more likely to lose their symptoms and have normal lung function at puberty.[23] In MAS, allergic rhinitis in preschool children is a predictor for subsequent wheezing onset.[24] In CAPS (USA), children with atopic eczema were more likely to have a history of food allergies, allergic rhinitis, and current wheeze.[25] A substantial degree of asthma, rhinitis and eczema comorbidity was observed in ECA (Norway) and BAMSE (Sweden). [26,27]

Pediatricians are frequently asked to predict the future course of wheezing and asthma in individual subjects. However, prognosis in an individual patient is difficult.[28] The asthma predictive index[13] is effective for groups of subjects and has been proposed for individual subjects.[29] In ECA, combining IgE to inhalant allergens and severity of airways obstruction at 2 years was superior in predicting asthma at 10 years than either alone.[30] However, current prediction algorithms aiming to identify individual preschool children having asthma at school age are still of modest diagnostic value.[31]

Unmet needs

There is no consistent evidence that clinical phenotypes correspond to genuine biological entities that reflect specific interactions between genes and environment. These phenotypes may reflect a continuum of states rather than discrete entities. Exploration of new phenotypes eventually may result in a refined classification of phenotypes that more closely reflects the relevant pathogenic mechanisms. The interplay among asthma, rhinitis and eczema is still poorly understood. Current asthma phenotypes are not amenable to primary prevention and their natural history cannot be reliably predicted. There is a need to consider alternative research approaches including the use of unsupervised statistical techniques with available data as well as integrative systems biology. Some initiatives like MeDALL[8,9] combine both approaches.

Research priorities

Broadly, research priorities could be classified in 3 groups (Table 3):

1. **Better characterization of phenotypes** including (a) a unique agreed upon classification of asthma that can be applied to research, diagnosis and treatment, (b) a better understanding of the interplay between asthma and allergy, (c) how allergic

phenotypes interrelate across the life cycle, and (d) if extreme phenotypes can be defined. [8,9]

2. **Natural history and its determinants.** There is a well-established relationship between lung function impairment and chronic wheezing and asthma. However, links to new onset and chronic asthma in adults and to COPD are of great interest but need more data.[32]

Another relevant aspect concerns risk stratification and risk prediction as current models lack sufficient accuracy to be of clinical use at the individual level.

3. **Pathogenesis.** Understanding the mechanisms of asthma and allergies from early life to the elderly (across the life cycle) is an important requirement for a better understanding of phenotypes and their natural history (i.e., expression, progression, and remission). There is a close interaction between clinical and epidemiological research.

Workgroup 2: Asthma Risk Factors (group membership: Table 1)

The contribution of birth cohort studies to understand risk and protective factors

Numerous environmental determinants have been assessed in birth cohorts: exposure to environmental tobacco smoke, ambient air pollution, and indoor factors such as household chemicals, molds, and water damage. Environment plays a role during pregnancy and across the life cycle.[33] Early animal exposure, such as keeping a dog may be protective,[34–36] but a meta-analysis[37] showed overall no protection with pet exposure. Consistent protective associations were reported for growing up in a farming environment,[35] while consistent adverse associations were found for living in homes with visible molds.[1] Some gene-environment interactions have been detected. For example, in the Isle of Wight cohort (UK), an interaction between maternal smoking during pregnancy and regions of the IL-13 gene (SNP: rs20541) was reported in persistent childhood asthma.[38] In CCAAPS (USA), an association between traffic exposure and persistent wheezing during childhood was modified by endotoxin exposure.[39]

Lifestyle has been studied in many cohorts such as day care, parental smoking, parental stress, and psychosocial factors; dietary factors such as maternal allergen intake, vitamin D and antioxidant ingestion in pregnancy, breastfeeding, hydrolysed formula feeding, bottle-feeding in bed, introduction of solids and fish intake, introduction of probiotics and obesity. In ACCESS, independent effects of prenatal and postnatal maternal stress on repeated wheeze risk were found in children followed to age 2 years.[40] In the Viva cohort (USA), a greater risk for recurrent wheeze at age 2–3 years was predicted by lower birth weight, greater increase in weight-for-length in the first 6 months of life, and adiposity.[41] In the combined GINIplus and LISAplus cohorts (Germany), rapid weight gain velocity was associated with an increased risk for asthma until age of 10.[42] This finding was replicated using data from 8 European birth cohorts.[43]

Viral or bacterial diseases and infections may be a risk or a protective factor for developing wheeze, asthma, and allergic diseases.[44] Particular attention has been given to respiratory syncytial virus (RSV) and human rhinovirus (HRV) infections. In COAST (USA), HRV

wheezing in the first 3 yrs of life was a highly significant risk factor for the development of asthma[45], and this risk was significantly increased based on genetic variation at the 17q21 locus.[46] Allergic sensitization further enhanced this risk,[45] but interestingly, this increase in risk was independent of genetic variation at the 17q21 locus. Endotoxin may be a biomarker for complex microbial exposures. High home endotoxin levels protect against allergic sensitization in farm and urban settings, whereas, in urban settings (EHAAS, USA) endotoxin increased early wheeze risk.[47,48] The microbiome in the gastrointestinal tract, the respiratory tract, the skin and the environment has received much attention, but data from cohort studies are very few and mostly relate to the gut microbiome and the development of atopic dermatitis. [49–52]

Unmet needs

The prospective design of birth cohort studies allows the investigation of the temporal relation between environmental exposures and the new onset of disease. Exposures occurring before the inception of disease suggest causal factors. The translation of these findings to primary and secondary prevention is a major goal and future studies should focus and interrogate factors that are promising and amenable to prevention and intervention trials. Birth cohort studies can ideally inform later trials by:

- Investigating the relevant time windows of exposures through repeated measurements starting in pregnancy,

- Assessing the individual and cumulative dose of exposures at these repeated time periods, and

- Assessing the relevance and importance of various covariates and context dependency (race, ethnicity, geography, age) of any observed risk and protective exposures.

Research priorities

1. Birth cohort studies that include biological measures can investigate responses to environmental exposures (e.g. immune responses, gene-environment interactions). Such inbuilt mechanistic aspects will help understand whether risk and protection is limited to particular subpopulations that might need to be targeted in subsequent intervention trials.

2. In future and current (CHILD, WHEALS) studies, the new technologies for exposure assessment such as high throughput techniques for microbial exposures on body surfaces and the environment, and the intrinsic 'omics' determinants, will create large and complex data sets of interrelated measures of exposure ('exposome') and intrinsic determinants of disease (genome, metagenome, transcriptome, etc.).

3. Novel statistical analytical techniques such as unsupervised approaches and systems biology must be developed and applied to the vast amount of collected data.

Workgroup 3: Immune development (group membership: Table 1)

The contribution of birth cohort studies to understand immune development

Immune responses at birth are related to risk factors for developing wheezing, asthma, lower respiratory tract infection, allergic sensitization and atopic dermatitis in infancy. Even so, reconciling birth cohort findings is hindered by the complexity involved in immunologic predictors, their measurement, developmental changes, and uncertainties in outcomes definitions such as wheezing and asthma phenotypes, and differences in methodology among investigators. Distinct immunologic patterns are associated with different outcomes previously considered collectively under the umbrella of atopy.[53] This complexity, along with technical limitations in the standardization of assays, has presented a major challenge to understanding the relationship between immune development and asthma.

A bias towards Th2 responses at birth is consistently associated with subsequent IgE sensitization and wheezing. The purported Th2 bias may be better described as generally low mononuclear cell responses to mitogens and allergens, with a more pronounced reduction in interferon-gamma (IFN-γ) responses. After birth, children with recurrent wheezing may develop enhanced Th1 responses, while the Th2 responses remain a risk factor for asthma. Accordingly, early sensitization to allergenic proteins indicates increased risk of wheezing and asthma.[54] This relationship is not dichotomous and is influenced by quantitative and qualitative measurements of allergic sensitization.[17]

Early patterns of immune development and allergic sensitization influence the subsequent risk for wheezing and asthma.[55] Prenatal and early postnatal factors modify early immune development. These include, but are not limited to, family history, race, season of birth, maternal smoking, mode of delivery, size at birth, diet, bioactive environmental exposures, and day care.[56,57] Studies in animal models and in infants and children suggest that microbial effects may act on innate immunity and/or metabolic pathways and subsequent sensitization to allergens, airway responses to infections, and eventual asthma.

Environmental factors influence the epithelium and innate immune elements to modify adaptive immunity and these mechanisms appear to be relevant to the development of airway inflammation and asthma.[58]

Unmet Needs

A number of technologic advances would facilitate future research efforts not only for the research in immune development of asthma and allergy.

- Many assays of innate and adaptive immune responses are potentially useful, but require optimization and standardization. Examples include generalized measures of cellular responses to innate and adaptive stimuli, and especially assays providing information about cell-specific responses. For example, tetramer technology could enable tracking of T cell responses in an organ specific manner.[59] Standardized protocols, quality control checks, and pools of standardized reagents are necessary first steps.

- Comprehensive systems biology approaches[60] offer the promise of providing unbiased insights into biologic networks associated with asthma.[61] Examples include measurements of the lung and gut microbiome, gene coexpression networks, epigenetic changes, metabolomic approaches focusing on airway-derived fluids, and protein and epitope mapping of allergen-specific IgE and IgG responses. Data from studies utilizing these technologies are needed to gain a holistic understanding of environmental effects on immune development and the development of asthma.

- New technologies are needed to provide information about lung immunity and asthma.[62] Do upper airway responses, which are easily accessible, provide an informative model of immune changes in the lung in early life? Identification of new biomarkers that reflect lung immune development and airway inflammation is an important research objective.

- Development of integrative statistical methodology is needed for datasets that are complex, voluminous, and contain both immune measurements and a host of clinical data. Statistical methods are needed to account for repeat sampling, time and age effects, and to distill huge datasets from systems approaches into conceptual advances that can be translated into novel therapeutic targets. Observational studies and systems biology approaches can generate reams of data, but lack of appropriate high-throughput data processing methodology represents a considerable bottleneck to progress.

Research priorities

Three specific areas of investigation relate to this central theme.

1- In-depth studies on the postnatal maturation of systemic adaptive and innate immune function during early life are required, incorporating (where feasible) both systems-level and epigenetic analyses. These studies should include the functions of a range of "orphan" cell populations that have received limited attention in previous birth cohort studies. These include, but are not restricted to, neutrophils, cytolytic T-cells, NK cells, dendritic cells and TREC-positive recent thymic emigrants that dominate the circulating neonatal T-cell compartment. Studies should specifically analyze the maturation of respiratory mucosal immune function, exemplified by secretory IgA responses in saliva and nasal washes. Both systemic and local immunity in the airways should be broadened to encompass situations in which the steady state is perturbed by environmental challenges known to be associated with asthma risk, typified by respiratory viral infections.

2- Studies focusing on bidirectional interactions between the microbiome and the host in relation to immune maturation and asthma[63] should be at a holistic level and encompass the three major tissue compartments: gastrointestinal tract, respiratory tract and skin. The key questions relate to colonization effects (qualitative/quantitative/kinetic) on metabolic pathways and immunological and clinical outcomes, identification of specific bacteria within complex exposures that are associated with beneficial effects, modulation of acute viral respiratory infections on host immune responses, modulatory effects of host immune

responses on microbiome components at baseline and during episodic airways inflammation, and on the subsequent development and progression of asthma and related phenotypes.

3- Major underlying effects of gender on asthma risk may be mediated partly by sex-related differences in immune maturation that are poorly characterized. These effects may manifest throughout childhood, before, during and after puberty. Additional studies on gender specific immune development are needed.

Workgroup 4: Pulmonary Development (group membership: Table 1)

Contribution of birth cohort studies to understand the impact of early lung function for later allergic diseases

Low lung function in early life is associated with low function in adulthood, an increased risk of wheeze in infancy and preschool children, and an increased risk of asthma in childhood.[20,21,64–66] Male gender and maternal smoking during pregnancy increase the risks.

Reduced peak flow values have been found already in pre-school children exposed to high traffic related air pollution, supporting findings in later childhood.[67]

The most predictive pulmonary function measurements are those that assess expiratory flow at a given lung volume. Increased AHR in infancy is associated with adverse respiratory outcomes in early childhood, but this association may decline with increasing age.[64,68]

Methodology to assess early pulmonary function in birth cohorts

Methods depend on the research question, ethical issues, anticipated cohort size, and resources available, as some of the most informative tests are more expensive to perform, require special expertise and sometimes sedation, and commercial equipment is not always available.

- **The raised volume forced expiration** technique provides the most reproducible and useful information on airway and pulmonary function.[69,70] Its comparability to forced expiration measurements used later in childhood allows better longitudinal comparisons. However, it usually requires the infant to be asleep with sedation and ethics committees often require a paediatrician to be present. Further studies are needed to determine if the values early in life are influenced by increased airway tone or are secondary to smaller-sized airway lumen or lower pulmonary elastic recoil.

- **The tidal forced expiratory flow technique**[71] predicts respiratory outcomes in several long-term studies,[20] and is easier to perform than raised volume forced expiration.

- **Tidal breathing flow pattern** assessments have the advantage of being quicker to perform, do not require sedation and can be performed in awake as well as sleeping babies. Tidal breathing techniques would appear to be more subject to variation in breathing patterns unrelated to underlying airway and lung structure, but in practice, results derived can provide similar future associations[19] to those of forced

expiration. The ratios derived from tidal breathing patterns predict respiratory outcomes.[19]

- **Airway responsiveness** assessments are more time consuming to perform than baseline respiratory function tests. Inhalation challenge using histamine and methacholine in early life can predict respiratory outcomes in childhood,[64,68] but the physiological mechanisms that contribute to AHR or the relationships with future outcomes are unknown. Given the difficulties in matching agonist dose for the size of the subject, comparisons between subjects of very different sizes are best avoided, although for cohorts reviewed at specific ages, valid longitudinal comparisons can be made by evaluating ranked data.[21]

- **Responses to β-2 adrenergic agonists** have not been performed in neonatal cohort studies. In older infants, increased bronchial tone can be present prior to any wheeze episodes,[72] but bronchodilator response of infants with history of wheeze has been inconsistently associated with asthma risk.[73,74]

- **Forced oscillation technique (FOT)** is useful in preschool children and can be performed with minimal cooperation, but is less applicable in children less than two years of age. When performed in birth cohort studies, reported results are comparable to those obtained by spirometry.[75,76]

- **Lung clearance index** (LCI) providing information on ventilation inhomogeneity in the lung can be assessed using the multiple breath inert gas washout technique with tidal breathing. LCI has been used to detect airway disease in infants with cystic fibrosis.[77,78] LCI is being evaluated in a neonatal cohort study of asthma but results are not yet available. However, LCI may be more useful as a marker of disease than of airway or lung development.

Methodology to assess other related outcomes in birth cohorts

- **Fractional exhaled nitric oxide (FeNO)** has been assessed in many birth cohorts. While there have been some relationships to wheezing early in life,[79,80] levels may be more related to IgE sensitization than asthma.[81] In addition, the on-line and off-line measurements used in infants may not adequately approximate the standardized technique used in older cooperative subjects,[82,83]

- **Lung imaging** has rapidly advanced in recent years. High resolution computerised tomography (HRCT) scans produce excellent resolution with substantially lower radiation exposures and scanning times short enough to avoid general anaesthesia.[84] Magnetic resonance imaging (MRI) can assess lung growth and development *in utero*, as well as *extra utero* without ionizing radiation.[85,86] Further development of both HRCT and MRI may allow pulmonary assessment early in life for birth cohort studies. However, imaging neonates during tidal breathing are limited to only the first few airway generations where quantitative measurements of airway size and wall thickness can be obtained, and ideally, lung volume will need to be standardized using the augmented-breath hold technique, which requires sedation.[87,88]

Unmet needs

- There is a need for the development of additional physiologic and imaging techniques to assess infants without sedation and with minimal or without ionizing radiation.

- There is a need to integrate respiratory functional and structural assessment with immunologic, cellular, molecular, and genetic information.

Research priorities

1. Pre-morbid pulmonary dysfunction occurs very early in life and is associated with asthma symptoms in childhood; however, trajectories and physiologic mechanisms for different phenotypes are not well understood.

2. Pulmonary function assessments should be done as part of future birth cohort studies whenever possible, since the contribution of initial pulmonary function to asthma-related outcomes is needed when evaluating other risk factors.

3. Systems biology studies using assessments of molecular and cellular biology, genetics, proteomics, immunological responses and microbiome are needed to elucidate the mechanisms that affect pulmonary development.

Workgroup 5: Networking and Harmonization (group membership: Table 1)

Needs for harmonized birth cohorts

Over 130 birth cohorts with data on asthma and allergy have been initiated in the world over the past 30 years. The timing of the establishment of these cohorts is critical as they span the time period of a dramatic increase in these diseases. The information gathered is remarkable, but data are in isolated, independent databases. Although the assessment methods of the studies vary, most cohorts were established and followed using rigorous methodology and data are usually available in electronic format. Most cohorts will follow children up to adulthood. Since 2004, several research initiatives funded under the EU FP6-FP7 have attempted to identify, compare and evaluate pooling data from existing European birth cohorts (GA[2]LEN,[7,89–90] ENRIECO,[1,2] CHICOS[2] and MeDALL[8,9]). The growing networking capacity of birth cohort studies needs to be expanded to other countries, made sustainable, and the cumulative learning of successive projects facilitated.[3] Further, as old cohorts continue follow up and new cohorts are developed, it would be optimal to collect data in a standardized fashion that would allow either comparison or the harmonization of essential core elements. Several reasons favour harmonization of existent questionnaires and the pooling of established and future birth cohorts (Table 4).

Definition of the term "birth cohort"

Epidemiologists use the term "cohort" to describe a group of persons who are observed over a period of time, commonly multiple years. An observational "cohort study" is an epidemiologic study of individuals who are exposed in different degrees (or not exposed at all) to a risk or protective factor hypothesized to influence the occurrence of a given disease or outcome. Terms such as follow-up, longitudinal, and prospective study, describe essential features of an observational cohort study.[91]

The term "birth cohort study" is generally used to describe a cohort study where study subjects (newborns, infants) were recruited shortly after birth (sometimes mothers were approached already during pregnancy) and observed over many years to examine associations between early life exposures and childhood outcomes.

The term "interventional" birth cohort study has been used occasionally. It refers to investigations where newborns (often at high-risk e.g. from allergic parents) were recruited for evaluating the efficacy of a preventive measure. Many epidemiologists would not describe such an approach as a cohort study (not purely observational anymore) but rather as an intervention study. This type of study is an experiment, e.g. a randomized or non-randomized controlled trial, in which subjects are allocated into groups, to evaluate the efficacy and safety of a preventive or therapeutic regimen.[91] Such studies have also been used to evaluate etiological factors for allergic disorders. However, direct pooling of data from observational and interventional studies is not advisable, as inclusion and exclusion criteria and protocols from such studies usually differ considerably. Furthermore, interventions, even placebo, may have influenced the occurrence of disease, making it difficult to properly evaluate associations between exposures and occurrence of these diseases. Depending on the specific research question, however, separate pooling of data from either observational or intervention studies may be desirable and operating definitions can be discussed during harmonization meetings.

Systematic review on birth cohorts

A systematic review aimed to identify, appraise, select and report all high quality evidence concerning birth cohorts in allergy and asthma was initiated around the world using an exhaustive summary of literature.

How harmonization of birth cohorts can be done?

The complexity and work load of harmonizing research protocols and databases, in part or in total, needs to be addressed with a well-planned agenda of long-term initiatives and investigator and programming resources. The numerous institutional and ethical issues underlying large networked studies should be identified and addressed. These challenges are complex, demanding and require research strategies to reduce fragmentation and facilitate the incorporation of lessons learned from studies so they are effectively passed into the next ones.[2] MeDALL has started to harmonize 123 clinical questions and a workshop was held in Barcelona November 6–9, 2012 to finalize the process.

Uniform core questionnaire for birth cohorts on asthma and allergy

MeDALL (www.medall-fp7.eu) has developed a uniform questionnaire translated in 6 languages and available online. This questionnaire is interoperable with the harmonized questions so that historical and newly collected data may be compared.[92]

Research priorities

The discussion during the workshop showed the difficulties that can be encountered in pooling existing data. In particular, funding and ethical issues were clearly identified. Workshop participants indicated that ethical issues must be carefully considered and there

needs to be an Ethics Work Package as well as an Ethics Advisory Board in the project. Another important aspect was the trust of the different cohort PIs to release data to other investigators. This has also been taken into account in GA^{2}LEN and further expanded in MeDALL to preserve privacy of data.

On the other hand, the importance of pooling data in order to better answer etiological questions was recognized, as well as the possibility of developing a uniform questionnaire which could be used in ongoing or new studies and could be linked with existing historic data.

Conclusions

Existing population-based birth cohorts have contributed to our knowledge of the development of asthma and atopy in many areas such as: (1) characterizing different wheezing phenotypes, (2) documenting the differing onset of aeroallergen reactivity, (3) describing the natural history of asthma and pulmonary functions, (4) noting the importance of early life risk factors such as lower lung function or pre- and post-natal ETS exposure and the later development of asthma, and (5) identifying gene-environment interactions such as the RSV 17q21.

Collaboration across population-based asthma birth cohorts can provide information when findings from individual cohorts are inconclusive or contradictory. Harmonization across existing and newly created birth cohorts will facilitate these types of analyses. A number of collaborative efforts involving multiple birth cohorts have already occurred. The topics have included pet ownership,[37] maternal smoking in pregnancy,[93] and mold and dampness,[1] and the link between weight gain and asthma.[43] These efforts demonstrate how collaboration across cohorts can provide adequate sample sizes to answer research questions. The availability of the publically accessible dataset (AsthmaBirthCohorts.niaid.nih.gov and www.medall-fp7.eu) that was developed as part of this workshop will provide researchers with information to establish future research collaborations.

New birth cohorts will be needed to apply new technologies to current research interests, to provide data on new research interests and the impact of ongoing societal changes. The MeDALL allergen-chip, which can evaluate the IgE and IgG reactive profiles of more than 170 allergen molecules, is now available to more completely characterize the allergic status of an individual.[94] New technologies are now available to more accurately and completely characterize the microbiome. However, stored samples from existing cohorts will not be sufficient to fully investigate this issue. Exposure to a Western lifestyle has been an area of considerable interest in asthma and allergy. A number of countries around the world (e.g. in Eastern Europe and Asia) are in transition to a more Western style of life. Birth cohorts in these countries could help us better understand how these changes will impact future asthma and allergy rates.

The five workgroups have identified many areas of future research interest. Establishing criteria for asthma phenotypes that are mechanistically-based and reflect biological entities, including degrees of severity, are the highest priority. Other research priorities include

investigations to define the natural history and determinants of disease and underlying mechanisms of the various asthma phenotypes. Incorporation of pulmonary function and\or structure measurements and measurements of immune development are strongly encouraged in all birth cohorts. Further technical development will be necessary to make this possible. Innovative statistical approaches such as systems biology approaches should be utilized for analysis of complex datasets created by cohort studies. Efforts to harmonize data of the different cohorts are just beginning, and appear to be important steps towards understanding similarities and differences related to exposures, outcomes and phenotypes around the world. The panel concluded that a combination of investigator leaders and novel ideas is required to move forward towards achieving these goals and objectives. Future directions include expanding the reach of existing cohorts into other chronic diseases as the participants age. A follow up meeting on this topic was held in Montpellier, France in December, 2013.

Acknowledgments

Abbreviations

ACCESS	Asthma Coalition on Community, Environment, and Social Stress
AHR	Airway hyper-responsiveness
ALSPAC	Avon Longitudinal Study of Parents and Children
BAMSE	Barn (Children), Allergy, Milieu, Stockholm, Epidemiological Study
CAPS	Childhood Asthma Prevention Study
CCAAPS	Cincinnati Childhood Allergy and Air Pollution Study
CHICOS	Developing a Child Cohort Research Strategy for Europe, FP7
CHILD	Canadian Healthy Infant Longitudinal Development
COAST	Childhood Origins of ASThma study
COPD	Chronic Obstructive Pulmonary Disease
ECA	Environment and Childhood Asthma
EHAAS	Epidemiology of Home Allergens and Asthma
ENRIECO	Environmental Health Risks in European Birth Cohorts, FP7
FeNO	Exhaled Nitric Oxide
FOT	Forced Oscillatory Technique
FP6,FP7	Framework Program for Research and Technological Development 6, 7

GA²LEN	Global Allergy and Asthma European Network, FP6
GABRIEL	A multidisciplinary study to identify the genetic and environmental causes of asthma in the European Community
GINIplus	German Infant Nutrition Intervention plus environmental and genetic influences on allergy development
HRCT	High resolution computerised tomography
HRV	Human rhinovirus
Ig	Immunoglobulin A, E, G
IFN-γ	Interferon-gamma
ISAAC	International Study of Asthma and Allergies in Childhood
LCI	Lung clearance index
LISAplus	Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus Air Pollution and Genetics
MAAS	Manchester Asthma and Allergy Study
MAS	Multi-centre Allergy Study
MeDALL	Mechanisms of the development of allergy
MRI	Magnetic Resonance Imaging
NHLBI	National Heart, Lung and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NK	Natural killer cells
PIAF	Perth Infant Asthma Follow-up
PIAMA	The Prevention and Incidence of Asthma and Mite Allergy -Natural History Study
SNP	Single Nucleotide Polymorphisms
RSV	Respiratory Syncytial Virus
SAGE	Study of Asthma Genes and the Environment
TH1	T helper cell 1
TH2	T helper cell 2
TREC	T-cell Receptor Excision Circle

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Table 1

Participants in Workgroups

Clinical Phenotypes Workgroup	Asthma Risk Factors
Chair: Fernando D. Martinez, M.D. Co-Chair: Josep M. Anto, M.D., Ph.D. Members: J. Henderson, M.D. Allan Becker, M.D. Joachim Heinrich, Ph.D., M.Sc. Robert Wood, M.D. D. Bernstein, M.D. Dennis R. Ownby, M.D.	Chair: Erika R.M. von Mutius, M.D., M.Sc. Co-Chair: Robert F. Lemanske Jr., M.D. Members: S. Hasan Arshad, D.M. Diane R. Gold, M.D., M.P.H. Kathleen Belanger, Ph.D. Malcolm R. Sears, M.B., Ch.B. Angela Simpson, M.D., Ph.D. Xiaobin Wang, M.D., M.P.H., Sc.D. Kecia N. Carroll, M.D., M.P.H. Philip J. Cooper, Ph.D. Anita Kozyrskyj, Ph.D.
Immune Development	**Pulmonary Development**
Chair: James E. Gern, M.D. Co-Chair: Patrick G. Holt, Sc.D. Members: Anne L. Wright, Ph.D. Rudy Valenta, M.D. Dan J. Jackson, M.D. Mario Castro, M.D., M.P.H. Rachel L. Miller, M.D. Len B. Bacharier, M.D.	Chair: Robert Tepper, M.D., Ph.D. Co-Chair: Peter N. Le Souef, M.D. Members: Rosalind J. Wright, M.D., M.P.H. Scott T. Weiss, M.D., M.S. Padmaja Subbarao, M.D., M.Sc. Karin Lodrup-Carlsen, M.D., Ph.D. Wayne J. Morgan, M.D.
Networking and Harmonization	**On paper but not on working group**
Chair: Jean J. Bousquet, M.D. Co-Chair: Christine Cole Johnson, Ph.D. Members: Thomas Keil, M.D., M.Sc. Matthew Gillman, M.D., S.M. Michael Cabana, M.D., M.P.H. Patrick Ryan, Ph.D. Soo-Jong Hong, M.D., Ph.D. Debra Stern, M.S. Anna Bergstrom, Ph.D. Isabelle Momas, Ph.D. – non attendee H.A. (Jet) Smit, Ph.D.	Mariona Pinart, Ph.D.

Table 2

Request for Information sent to Birth Cohorts Prior to the meeting

Clinical Phenotypes Workgroup

1   Which are the main asthma phenotypes you have identified in your birth cohort? Please provide a definition of these phenotypes.

2   Which are the more relevant new findings you have published so far about the asthma phenotypes in your cohort? Please mention up to 5 (each) about these phenotypes/risk factors.

3   Has your birth cohort contributed to any relevant methodological development in regards to phenotypes? Please specify.

4   Which are the main priority areas for future research in birth cohorts regarding asthma phenotypes?

Asthma Risk Factors Workgroup

1   Which are the more relevant new findings you have published so far about the risk factors for asthma in your cohort? Please mention up to 5 (each) about these risk factors.

2   Has your birth cohort contributed to any relevant methodological development in regards to risk factors? Please specify.

3   Which are the main priority areas for future research in birth cohorts regarding asthma risk factors?

Immune Development Workgroup

1   Which are the main immunologic outcomes you have measured in your birth cohort and at what ages?

2   Which are the more relevant new findings you have published so far about immune development in your cohort? Please mention relationships to wheezing, asthma, and allergic sensitization.

3   Has your birth cohort contributed to any relevant methodological development for immune assessments? Please specify.

4   Which are the main priority areas for future research in birth cohorts regarding immune development and asthma? Include suggestions related to technologic advances and study designs.

Pulmonary Development Workgroup

1   What pulmonary outcomes have you included in your birth cohort and at what ages?

2   Which are the more relevant new findings you have published so far about the pulmonary development in your cohort?

3   Has your birth cohort contributed to any relevant methodological development in regards to pulmonary development? Please specify.

4   Which are the main priority areas for future research in birth cohorts regarding pulmonary development?

Networking and Harmonization Workgroup

1   Harmonization efforts to date (current MeDALL focus on Phenotypes)

2   Future harmonization efforts

3   Develop a harmonized questionnaire for the comparability of existing birth cohort studies

Table 3

Research priorities of clinical phenotypes

Better characterization of clinical phenotypes
Allergic vs non allergic phenotypes
Comorbidity of allergic phenotypes
Unsupervised phenotyping (using cluster, LCA and other methods)
Environmental induced phenotypes (air pollution, low chemical dose, etc.)
Risk factors of severity and difficult to treat wheezing
Stratified medicine approach in asthma
Evolution & validation of new of phenotypes
Gender, race and genetics as phenotypical determinants
Computational models for complex data/multifactorial assessment of risk factors
Natural history and its determinants
Long term patterns of airflow limitation from early life to late adulthood and COPD
Role of lung function in assessing the phenotypes
Risk prediction and severity scores
Natural history (puberty, gender, race/ethnicity, minorities, etc.)
Influence of antenatal and in utero risk factors on phenotypes
Mechanisms of asthma and allergies
Genomic (genes and epigenetics) determinants
Overweight, obesity, growth, fat distribution and related mechanisms
Biomarkers
Immunological mechanisms and immunophenotyping
Vitamin D
Gut microbiome
Stress and neurophenotyping
Microbiome and its interactions with immunological mechanisms

Table 4

Reasons favouring harmonization of existent questionnaires and the pooling of established and future birth cohorts

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- Improving the assessment of the consistency of findings across various populations and facilitating research explaining heterogeneous results from analyses of individual cohorts

- Achieving the statistical power needed to assess both genetic and environmental determinants and their interactions

- Assessing the life course of subgroups of allergic and asthmatic phenotypes including economic burden and quality of life associated with rare but very severe phenotypes

- Determining gender-specific differences across different cultures and regions

- Broadening the diversity of environmental exposures as represented in different geographic settings (dietary, inhalant, socio-economic factors)