Workshop summary

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

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Population-based birth cohorts on asthma and allergies increasingly provide new insights into the development and natural history of the diseases. More than 130 birth cohorts focusing on asthma and allergy have been initiated in the last 30 years. A National Institute of Allergy and Infectious Diseases; National Heart, Lung, and Blood Institute; Mechanisms of the Development of Allergy (MeDALL; Framework Programme 7 of the European Commission) joint workshop was held in Bethesda, Maryland, on 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 article 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, the type of data collected at differing ages, and a selected bibliography provided by the participating birth cohorts. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

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

Work has begun to pool information across birth cohorts.[3] An Asthma Birth Cohort Workshop was held in Bethesda, Maryland,

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Abbreviations used
AHR: Airway hyperresponsiveness
ECA: Environment and Childhood Asthma
FP6: Framework Program for Research and Technological Development 6
FP7: Framework Program for Research and Technological Development 7
GA^{2}LEN: Global Allergy and Asthma European Network
GINIplus: German Infant Nutrition Intervention plus environmental and genetic influences on allergy development
LCI: Lung clearance index
MAS: Multi-centre Allergy Study
MeDALL: Mechanisms of the Development of Allergy
NHLBI: National Heart, Lung, and Blood Institute
NIAID: National Institute of Allergy and Infectious Diseases

on September 11-12, 2012, to further improve our understanding of existing asthma birth cohorts. 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 and Mechanisms of the Development of Allergy (MeDALL; Framework Program for Research and Technological Development 7 [FP7], European Commission). The workshop allowed epidemiologic, clinical, and laboratory researchers conducting research on asthma and other allergic diseases in birth cohorts to meet in order 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 the preidentified topics of asthma phenotypes, risk factors, immune development, and pulmonary development. The fifth workgroup worked to identify approaches for data pooling and harmonization (Table I). 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 II). 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 input obtained from the meeting attendees. Additional information gathered as part of the workshop is available at the National Institute of Allergy and Infectious Disease (AsthmaBirthCohorts.niaid.nih.gov) and MeDALL (www.medall-fp7.eu) Web sites. At these sites, the reader will find the characteristics of the birth cohorts included in this report, the 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 I)

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

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

Unsupervised statistical techniques, such as latent class or cluster analyses, were used to identify and define asthma phenotypes.[8,9,14] Using latent class analysis in the Avon Longitudinal Study of Parents and Children (ALSPAC; United Kingdom) and Prevention and Incidence of Asthma and Mite Allergy–Natural History Study (PIAMA; The Netherlands), wheezing patterns were in agreement with the Tucson classification.[11,15,16] The Manchester Asthma and Allergy Study (MAAS; United Kingdom) 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 asthma and allergic phenotypes.[9]

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

In the Tucson birth cohorts, 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 age 10 years and with a low respiratory function at the age of 22 years.[19,20] Lung function patterns have been studied in the Perth Infant Asthma Follow-up (PIAF) study (Australia), but the lung function impairment in children with transient wheeze was not replicated.[21]

The Multi-centre Allergy Study (MAS; Germany) did not show that exposure to inhaled allergens was a causal determinant of

TABLE I. Participants in workgroup

Clinical Phenotypes	Asthma Risk Factors
Chair: Fernando D. Martinez, MD	Chair: Erika R. M. von Mutius, MD, MSc
Co-Chair: Josep M. Anto, MD, PhD	Co-Chair: Robert F. Lemanske, Jr, MD
Members:	Members:
John Henderson, MD	S. Hasan Arshad, DM
Allan Becker, MD	Diane R. Gold, MD, MPH
Joachim Heinrich, PhD, MSc	Kathleen Belanger, PhD
Robert Wood, MD	Malcolm R. Sears, MB, ChB
David I. Bernstein, MD	Angela Simpson, MD, PhD
Dennis R. Ownby, MD	Xiaobin Wang, MD, MPH, ScD
	Kecia N. Carroll, MD, MPH
	Philip J. Cooper, PhD
	Anita Kozyrskyj, PhD

Immune Development	Pulmonary Development
Chair: James E. Gern, MD	Chair: Robert S. Tepper, MD, PhD
Co-Chair: Patrick G. Holt, ScD	Co-Chair: Peter N. Le Souëf, MD
Members:	Members:
Anne L. Wright, PhD	Rosalind J. Wright, MD, MPH
Rudolf Valenta, MD	Scott T. Weiss, MD, MS
Daniel J. Jackson, MD	Padmaja Subbarao, MD, MSc
Mario Castro, MD, MPH	Karin Lødrup Carlsen, MD, PhD
Rachel L. Miller, MD	Wayne J. Morgan, MD, CM
Leonard B. Bacharier, MD	

Networking and Harmonization	On paper but not on working group
Chair: Jean Bousquet, MD	Mariona Pinart, PhD
Co-Chair: Christine C. Johnson, PhD, MPH	
Members:	
Thomas Keil, MD, MSc	
Matthew W. Gillman, MD, SM	
Michael D. Cabana, MD, MPH	
Patrick H. Ryan, PhD	
Soo-Jong Hong, MD, PhD	
Debra A. Stern, MS	
Anna Bergström, PhD	
Isabelle Momas, PhD (nonattendee)	
Henriette A. Smit, PhD	

asthma,[22] a finding confirmed by other studies. However, in MAS, sensitization to inhaled allergens and persistence of sensitization during childhood were associated with persistence of wheezing at school age.[23] MAS showed that children with nonallergic 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 the Childhood Asthma Prevention Study (CAPS; United States), 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 the Environment and Childhood Asthma (ECA) study (Norway) and Barn (Children), Allergy, Milieu, Stockholm, Epidemiological Study (BAMSE; Sweden).[26,27]

Pediatricians are frequently asked to predict the future course of wheezing and asthma in individual subjects. However, determining 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 the ECA study, combining IgE levels to inhalant allergens and severity of airways obstruction at 2 years was superior in predicting asthma at 10 years than the use of either factor 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 the environment. These phenotypes could eventually reflect a continuum of states rather than discrete entities. Exploration of new phenotypes could eventually 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, such as MeDALL,[8,9] combine both approaches.

Research priorities

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

1. *Better characterization of phenotypes*, including (1) a unique agreed-upon classification of asthma that can be applied to research, diagnosis, and treatment; (2) a better understanding of the interplay between asthma and allergy; (3) how allergic phenotypes interrelate across the life cycle; and (4) whether 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 chronic obstructive pulmonary disease are of great interest but require more data.[32] Another relevant aspect concerns risk stratification and risk prediction because 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 old age (across the life cycle) is an important requirement for a better understanding of phenotypes and their natural history (ie, expression, progression, and remission). There is a close interaction between clinical and epidemiologic research.

WORKGROUP 2: ASTHMA RISK FACTORS (GROUP MEMBERSHIP: TABLE I)

The contribution of birth cohort studies to understanding 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

TABLE II. Request for information sent to birth cohorts before 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 findings (each) about these phenotypes/risk factors.
3. Has your birth cohort contributed to any relevant methodological development in regard 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 findings (each) about these risk factors.
2. Has your birth cohort contributed to any relevant methodological development in regard 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 regard 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

pregnancy and across the life cycle.[33] Early animal exposure, such as keeping a dog, might be protective,[34-36] but a meta-analysis[37] showed no overall protection with pet exposure. Consistent protective associations were reported for growing up in a farming environment,[35] whereas consistent adverse associations were found for living in homes with visible mold.[1] Some gene-environment interactions have been detected. For example, in the Isle of Wight cohort (United Kingdom), an interaction between maternal smoking during pregnancy and regions of the *IL13* gene (single nucleotide polymorphism rs20541) was reported in patients with persistent childhood asthma.[38] In the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS; United States), 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, breast-feeding, hydrolyzed formula feeding, bottle-feeding in bed, introduction of solids, and fish intake; introduction of probiotics; and obesity. In the Asthma Coalition on Community, Environment, and Social Stress (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 Project Viva cohort (United States), a greater risk for recurrent wheeze at age 2 to 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 German Infant Nutrition Intervention plus Environmental and Genetic Influences on Allergy Development (GINIplus) and Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus Air Pollution and Genetics (LISAplus) cohorts (Germany), rapid weight gain velocity was associated with an increased risk for asthma until age 10 years.[42] This finding was replicated by using data from 8 European birth cohorts.[43]

Viral or bacterial diseases and infections might be a risk or a protective factor for wheeze, asthma, and allergic diseases.[44] Particular attention has been given to respiratory syncytial virus and human rhinovirus infections. In the Childhood Origins of Asthma study (COAST; United States), human rhinovirus wheezing in the first 3 years 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 might be a biomarker for complex microbial exposures. High home endotoxin levels protect against allergic sensitization in farm and urban settings, whereas in urban settings (Epidemiology of Home Allergens and Asthma; United States), endotoxin increased early wheeze risk.[47,48] The microbiome in the gastrointestinal tract, respiratory tract, skin, and 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

TABLE III. Research priorities of clinical phenotypes workgroup

Better characterization of clinical phenotypes
Allergic vs nonallergic phenotypes
Comorbidity of allergic phenotypes
Unsupervised phenotyping (using cluster analysis, latent class analysis, and other methods)
Environment-induced phenotypes (eg, air pollution and low chemical dose)
Risk factors of severity and difficult-to-treat wheezing
Stratified medicine approach in asthma
Evolution and validation of new phenotypes
Sex, race, and genetics as phenotypic 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 chronic obstructive pulmonary disease
Role of lung function in assessing phenotypes
Risk prediction and severity scores
Natural history (eg, puberty, sex, race/ethnicity, and minorities)
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
Immunologic mechanisms and immunophenotyping
Vitamin D
Gut microbiome
Stress and neurophenotyping
Microbiome and its interactions with immunologic mechanisms

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, and age) of any observed risk and protective exposures.

Research priorities

1. Birth cohort studies that include biological measures can investigate responses to environmental exposures (eg, immune responses and 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 (Canadian Healthy Infant Longitudinal Development [CHILD] and Wayne County Health, Environment, Allergy, and Asthma Longitudinal Study) 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 (eg, genome, metagenome, and transcriptome).
3. Novel statistical analytic 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 I)

The contribution of birth cohort studies to understand immune development

Immune responses at birth are related to risk factors for 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 toward T_H2 responses at birth is consistently associated with subsequent IgE sensitization and wheezing. The purported T_H2 bias might be better described as generally low mononuclear cell responses to mitogens and allergens, with a more pronounced reduction in IFN-γ responses. After birth, children with recurrent wheezing might have enhanced T_H1 responses, whereas T_H2 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 can 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 in the 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 the tracking of T-cell responses in an organ-specific manner.[59]

TABLE IV. Reasons favoring harmonization of existing questionnaires and pooling of established and future birth cohorts

• 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 sex-specific differences across different cultures and regions
• Broadening the diversity of environmental exposures as represented in different geographic settings (dietary, inhalant, and socioeconomic factors)

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 using 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 data sets that are complex, voluminous, and contain both immune measurements and a host of clinical data. Statistical methods are needed to account for repeat sampling and time and age effects and to distill huge data sets 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 a 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, natural killer cells, dendritic cells, and T-cell receptor excision circle (TREC)–positive recent thymic emigrants that dominate the circulating neonatal T-cell compartment. Studies should specifically analyze the maturation of respiratory mucosal immune function, as exemplified by secretory IgA responses in saliva and nasal wash fluid. 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, as typified by viral respiratory tract infections.
2. Studies focusing on bidirectional interactions between the microbiome and the host in relation to immune maturation and asthma[63] should be carried out at a holistic level and encompass the 3 major tissue compartments: gastrointestinal tract, respiratory tract, and skin. The key questions relate to colonization effects (qualitative/quantitative/kinetic) on metabolic pathways and immunologic and clinical outcomes, identification of specific bacteria within complex exposures that are associated with beneficial effects, modulation of acute viral respiratory tract infections on host immune responses, modulatory effects of host immune responses on microbiome components at baseline and during episodic airways inflammation, and the subsequent development and progression of asthma and related phenotypes.
3. Major underlying effects of sex on asthma risk might be mediated partly by sex-related differences in immune maturation that are poorly characterized. These effects can manifest throughout childhood before, during, and after puberty. Additional studies on sex-specific immune development are needed.

WORKGROUP 4: PULMONARY DEVELOPMENT (GROUP MEMBERSHIP: TABLE I)

Contribution of birth cohort studies to understanding the effect 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 sex and maternal smoking during pregnancy increase the risks.

Reduced peak flow values have been found in preschool 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 might decrease 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 because some of the most informative tests are more expensive to perform and 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 with 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 pediatrician to be present. Further studies are needed to determine whether 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 both awake and 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 with histamine and methacholine in early life can predict respiratory outcomes in childhood,[64,68] but the physiologic 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 measured in neonatal cohort studies. In older infants, increased bronchial tone can be present before any wheeze episodes,[72] but bronchodilator response of infants with a history of wheeze has been inconsistently associated with asthma risk.[73,74]
- The forced oscillation technique is useful in preschool children and can be performed with minimal cooperation but is less applicable in children under 2 years of age. When performed in birth cohort studies, reported results are comparable with those obtained by using spirometry.[75,76]
- The lung clearance index (LCI), providing information on ventilation inhomogeneity in the lung, can be assessed by 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 might be more useful as a marker of disease than of airway or lung development.

Methodology to assess other related outcomes in birth cohorts

- Fraction of exhaled nitric oxide has been assessed in many birth cohorts. Although there have been some relationships to wheezing early in life,[79,80] levels might be more related to IgE sensitization than to asthma.[81] In addition, the online and offline measurements used in infants might not adequately approximate the standardized technique used in older cooperative subjects.[82,83]
- Lung imaging has rapidly advanced in recent years. High-resolution computed tomographic scans produce excellent resolution with substantially lower radiation exposures and scanning times short enough to avoid general anesthesia.[84] Magnetic resonance imaging can assess lung growth and development *in utero*, as well as *extra utero* without ionizing radiation.[85,86] Further development of both high-resolution computed tomography and magnetic resonance imaging might 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 in which quantitative measurements of airway size and wall thickness can be obtained, and, ideally, lung volume will need to be standardized by 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 or without minimal ionizing radiation.
- There is a need to integrate respiratory functional and structural assessment with immunologic, cellular, molecular, and genetic information.

Research priorities

1. Premorbid 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 carried out as part of future birth cohort studies when possible because 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, immunologic responses, and the microbiome are needed to elucidate the mechanisms that affect pulmonary development.

WORKGROUP 5: NETWORKING AND HARMONIZATION (GROUP MEMBERSHIP: TABLE I)

Needs for harmonized birth cohorts

More than 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 because 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 by 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 European

Union's Framework Program for Research and Technological Development 6 (FP6)–FP7 have attempted to identify, compare, and evaluate pooling data from existing European birth cohorts (GA^{2}LEN[7,89,90]; Environmental Health Risks in European Birth Cohorts, FP7 [ENRIECO][1,2]; Developing a Child Cohort Research Strategy for Europe, FP7 [CHICOS][2]; and MeDALL[8,9]). The growing networking capacity of birth cohort studies needs to be expanded to other countries and made sustainable, and the cumulative learning of successive projects needs to be facilitated.[3] Furthermore, 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 harmonization of essential core elements. Several reasons favor harmonization of existing questionnaires and the pooling of established and future birth cohorts (Table IV).

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 subjects 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 in which study subjects (newborns and 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 in which newborns (often at high risk, such as 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, such as a randomized or nonrandomized 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 etiologic factors for allergic disorders. However, direct pooling of data from observational and interventional studies is not advisable because inclusion and exclusion criteria and protocols from such studies usually differ considerably. Furthermore, interventions, even placebo, might 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 might 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 by using an exhaustive summary of the 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 and 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 from 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 into 6 languages and available online. This questionnaire is interoperable with the harmonized questions so that historical and newly collected data can 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 that an Ethics Work Package is needed in the project, as well as an Ethics Advisory Board. Another important aspect was the trust of the different cohort principal investigators 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 to better answer etiologic 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 prenatal and postnatal environmental tobacco smoke exposure, and the later development of asthma; and (5) identifying gene-environment interactions, such as the respiratory syncytial virus 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] 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 data set (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 in order to provide data on new research interests and the effect 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 a subject.[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 (eg, 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 affect future asthma and allergy rates.

The 5 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, is 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 used for analysis of complex data sets created by cohort studies. Efforts to harmonize data of the different cohorts are just beginning and appear to be important steps toward 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 toward 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.

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