Pooling Birth Cohorts in Allergy and Asthma: European Union-Funded Initiatives – A MeDALL, CHICOS, ENRIECO, and GA²LEN Joint Paper

Jean Bousquet[a]   Josep Anto[b]   Jordi Sunyer[b]   Mark Nieuwenhuijsen[b]
Martine Vrijheid[b]   Thomas Keil[c]   MeDALL Study Group
CHICOS Study Group   ENRIECO Study Group   GA²LEN Study Group

[a]University Hospital, Hôpital Arnaud de Villeneuve, Montpellier, France; [b]Centre for Research in Environmental Epidemiology (CREAL), Municipal Institute of Medical Research (IMIM-Hospital del Mar), CIBER Epidemiología y Salud Pública (CIBERESP), and Universitat Pompeu Fabra (UPF), Barcelona, Spain; [c]Institute for Social Medicine, Epidemiology and Health Economics, Charité University Medical Center, Berlin, Germany

Abstract

Long-term birth cohort studies are essential to understanding the life course and childhood predictors of allergy and the complex interplay between genes and the environment (including lifestyle and socioeconomic determinants). Over 100 cohorts focusing on asthma and allergy have been initiated in the world over the past 30 years. Since 2004, several research initiatives funded under the EU Framework Program for Research and Technological Development FP6-FP7 have attempted to identify, compare, and evaluate pooling data from existing European birth cohorts (GA²LEN: Global Allergy and European Network, FP6; ENRIECO: Environmental Health Risks in European Birth Cohorts, FP7; CHICOS: Developing a Child Cohort Research Strategy for Europe, FP7; MeDALL: Mechanisms of the Development of ALLergy, FP7). However, there is a general lack of knowledge about these initiatives and their potentials. The aim of this paper is to review current and past EU-funded projects in order to make a summary of their goals and achievements and to suggest future research needs of these European birth cohort networks.

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Introduction

Long-term birth cohort studies are essential to understanding the life course, early predictors, risk, and protective factors of allergy and the complex interplay between genes and the environment (including lifestyle and socioeconomic determinants). Over the past 30 years, a very large number of newborns have been included in community birth cohorts. Over 100 cohorts focusing on asthma and allergy have been initiated around the world and some have followed subjects up to adulthood. The information gathered by these birth cohorts has already significantly advanced our understanding of allergy and asthma, particularly for the first years of life. However, these data are scattered.

Since 2004, several studies funded under the EU Framework Program for Research and Technological Development FP6-FP7 have integrated birth cohort studies to address scientific issues that otherwise would have been beyond the capacity of single studies. These issues have included the following: (i) broadening the diversity of environmental exposures in Europe (dietary, inhalant, and socioeconomic factors), (ii) achieving the statistical power needed to assess both genetic and environmental determinants and their interactions, (iii) assessing the life course of subgroups of allergic and asthmatic phenotypes including economic burden and quality of life of rare but very severe phenotypes, (iv) determining gender-specific differences across different cultures and regions in Europe, and (v) facilitating research on underlying mechanisms explaining heterogeneous results among the cohorts.

Though most of these EU-funded initiatives are still at an early stage, they have enabled the identification of some challenges that need to be addressed. The growing networking capacity of birth cohort studies needs to be made sustainable and the cumulative learning of successive projects facilitated. The complexity and work load of harmonizing research protocols and databases need to be addressed with a well-planned agenda of long-term initiatives. The different strategies for analyzing networked databases, including decentralized meta-analysis and centralized analysis of pooled data sets, need to be carefully compared. The numerous institutional and ethical issues underlying large networked studies should be better identified and addressed. These challenges are complex and demanding and require research strategies to reduce fragmentation and help ensure that the lessons learned from previous studies are effectively passed on to the next ones.

The aim of the paper is to review current and past EU-funded projects in order to make a summary of their achievements and to propose future research needs. Funded initiatives on genomics (e.g. EAGLE: Early Genetics and Life course Epidemiology) [1, 2] will not be included in this paper since their aim is largely different and only few cohorts on asthma and allergy are included in the analyses. The European Study of Cohorts for Air Pollution Effects (ESCAPE), a project in which adult and some large GA²LEN birth cohorts with comprehensive environmental data perform combined data analyses, will not be developed in the present paper as it uses the same birth cohorts as GA²LEN and/or MeDALL. The collaborative FP7 translational research project EuroPrevall started a multicenter birth cohort study recruiting a total of over 12,000 newborns in 9 countries across Europe in 2005–2009 [3, 4], but was not included herein since it did not pool data from different cohorts.

GA²LEN (FP6) 2005–2009

GA²LEN

The Global Allergy and Asthma European Network (GA²LEN) is an FP6 Network of Excellence created in 2004 as a vehicle to ensure excellence in research, bringing together research and clinical institutions to combat fragmentation in the European research area and to tackle allergy globally. GA²LEN has benefited greatly from the voluntary efforts of researchers who are strongly committed to this model of pan-European collaboration. The network was organized in order to increase networking for scientific projects in allergy and asthma around Europe [5, 6]. It was completed in 2009 but it is self-sustained.

Goals of the GA²LEN Birth Cohorts Work Package

Some of the longest-running and most important European birth cohorts on asthma and allergy have started to collaborate with the primary aim to compare their study designs, recruitment strategies and criteria, and assessment of allergic and respiratory outcome parameters, as well as assessment of relevant exposure variables including lifestyle factors and indoor and outdoor environments (S. Lau, WP leader, and T. Keil, WP coordinator, both from Charité, Berlin). The secondary aim was to evaluate the possibilities of pooled data analyses in order to answer research questions that may not be sufficiently answered by individual birth cohorts alone (table 1).

Methods

GA²LEN created a common database including all relevant study characteristics of European observational birth cohort studies on asthma and allergic diseases with long-term follow-up [5, 6]. Intervention studies such as randomized controlled trials of newborns or of pregnant mothers investigating preventive measures, such as hypoallergenic milk formula or dust mite impermeable mattress covers, were excluded because intervention trials are designed with different intentions than the observational cohorts and usually include only children at high allergy risk. Birth cohorts were included regardless of sample size or whether the data had been analyzed previously. Cross-sectional studies were excluded, since their main purpose is to determine the prevalence of disease and generate hypotheses but not to examine temporal relationships.

Table 1. Major characteristics of the projects

	Start date	End date	Birth cohort project
GA^{2}LEN	2004	2010	To compare cohort study designs, recruitment strategies and criteria, and assessment of allergic and respiratory outcome parameters as well as assessment of relevant exposure variables including lifestyle factors and indoor and outdoor environments.
ENRIECO	2009	2010	To advance the knowledge on specific environment and health causal relationships by providing support to the exploitation of the wealth of data generated by past or ongoing pregnancy and birth cohorts.
CHICOS	2010	2012	To develop an integrated strategy for mother-child cohort research in Europe and to make recommendations for research action at the European level for the next 15 years.
MeDALL	December 2010	December 2014	To harmonize existing cohort data in order to pool them and propose unsupervised statistical analyses and to make follow-up assessments with identical questionnaires and clinical methods.

Results

An inventory was set up and currently contains information from 25 European birth cohorts with a special focus on asthma and allergy [7–9] (table 2) in 10 European countries. For a subjective assessment of asthma and allergic rhinitis symptoms, most birth cohorts applied the questions suggested by the International Study of Asthma and Allergies in Childhood (ISAAC) group [10], whereas the definition of eczema was not as homogeneous across the studies. Several cohorts performed lung function tests, but no comparable procedures were used. Data on sensitization to various aero- and food allergens were assessed by specific immunoglobulin E in serum in 18 studies, and by skin prick tests in 12 studies.

Three working groups for pooled birth cohort analyses of the individual participant data were established to examine determinants of pet ownership in European birth cohorts on asthma and allergy [9], the relationship between pet exposure in early childhood and asthma and allergy at school-age [11], as well as overweight in preschool children and the development of wheeze/asthma [Rzehak et al., in revision].

ENRIECO (FP7) 2009–2010

Goals

The overall aim of the European initiative Environmental Health Risks in European Birth Cohorts (ENRIECO) was to advance the knowledge on specific environment and health causal relationships by providing support to the exploitation of the wealth of data generated by past or ongoing pregnancy and birth cohorts

[55]. Though the ENRIECO project included more that 40 birth cohorts with different aims and focuses, most of the GA^{2}LEN birth cohorts on asthma and allergy were also included.

Methods

Developing an inventory of birth cohorts suitable for studying environmental health problems was an achievement of ENRIECO (http://www.birthcohortsenrieco. net). Several working groups performed case studies (pooled and meta-analyses) by harmonizing their data to answer specific research questions. Birth cohorts with data on asthma and allergies examined the impact of indoor environmental exposures such as mold and dampness [56] and pre- and postnatal tobacco smoke in older children and in infants. A comparison of strengths and limitations of a *centralized* and a *decentralized* approach of data pooling was initiated in ENRIECO based on case studies with different research questions. In the first approach, a statistician collected raw data from all cohorts and harmonized and analyzed all data centrally. In the decentralized approach, all participating cohort PIs agreed on a method of harmonizing variables and performing analyses that the statistician in each cohort team had to follow. In the latter approach, the cohorts did not have to give their raw data away, just report the final risk estimates to the central statistician for inclusion in the meta-analysis [Hohmann et al., in preparation].

Results

Data from 31,742 children from 8 ongoing European birth cohorts were collected and harmonized, led by T. Keil (Charité, Berlin). The subsequent meta-analysis per-

Table 2. Characteristics of European birth cohorts on asthma and allergy identified in GA²LEN

	Study acronym, start, setting	Study name	References	Recruited children, n	Main objectives	Principal investigators
1	Odense, 1985, Odense (Denmark)	Odense 1985 Birth Cohort	12	276	A, AR, E, food allergies, sensitization (natural course, risk factors)	A. Høst, S. Halken
2	Isle of Wight, 1989, Isle of Wight (UK)	Isle of Wight Study	13–17	1,456	A, E, food allergies (environmental factors)	H. Arshad, G. Roberts
3	MAS, 1990, Berlin, Düsseldorf, Mainz, Freiburg, Munich (Germany)	Multi-centre Allergy Study	18–21	1,314	A, AR, E, sensitization (natural course, risk factors)	S. Lau, T. Keil, U. Wahn
4	Leicester, 1990 cohort, Leicester (UK)	Leicester 1990 Cohort	22–24	280	A (natural course, risk factors of wheezing disorders)	C. Kuehni, M. Silverman
5	ECA, 1992, Oslo (Norway)	Environment and childhood asthma	25–28	3,754	A, AR, E (environmental factors)	K.C. Lodrup Carlsen, K.H. Carlsen
6	AMICS-Ashford, 1993, Ashford, Kent (UK)	Asthma MULTICENTRE Infant Cohort Study-Ashford	29, 30	642	A, AR, E (environmental factors)	P. Cullinan
7	BAMSE, 1994, Stockholm (Sweden)	Barn, Allergi, Miljo, Stockholm, en Epidemiologisk studie	31–34	4,089	A, AR, E (environmental factors)	M. Wickman
8	MAAS, 1995, Manchester (UK)	Manchester Asthma and Allergy Study	35, 36	957	A, AR, E (environmental factors)	A. Woodcock, A. Custovic
9	PIAMA-NHS, 1996, North, Central, West (The Netherlands)	The Prevention and Incidence of Asthma and Mite Allergy-Natural History Study	37–39	3,291	A, respiratory allergies (incidence, risk factors)	H.A. Smit, B. Brunekreef
10	GINI-B, 1996, Munich, Wesel (Germany)	German Infant Nutritional Intervention-Study (observational part)	40	3,739	A, AR, E, food allergies (natural course, environmental and other risk factors)	J. Heinrich, U. Krämer, A. von Berg
11	AMICS-Barcelona, 1996, Barcelona (Spain)	Asthma Multicentre Infant Cohort Study-Barcelona	29, 30	487	A, AR, E (environmental factors)	J. Sunyer
12	AMICS-Menorca, 1997, Island of Menorca (Spain)	Asthma Multicentre Infant Cohort Study-Menorca	29, 30	485	A, AR, E (environmental factors)	M. Torrent
13	LISA, 1997, Leipzig, Munich, Wesel, Bad Honnef (Germany)	Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood	41	3,097	A, AR, E, food allergies, sensitization (natural course, risk factors, East vs. West Germany)	J. Heinrich
14	SEATON, 1997, Aberdeen (UK)	Study of Eczema and Asthma To Observe the influence of Nutrition	42, 43	1,924	A, AR, E (diet)	A. Seaton, G. Devereux
15	Amnio Study, 1997, Southampton (UK)	Amnio Study		279	A, AR, E (cytokines/allergens in amniotic fluid)	J. Warner
16	DARC Study, 1998, Odense and surroundings (Denmark)	Danish Allergy Research Centre study	44	562	A, AR, E, food allergies (incidence, prevalence, risk factors)	C. Bindslev-Jensen
17	Leicester, 1998 cohort, Leicester (UK)	Leicester 1998 Cohort	22–24	4,247	A (natural course, risk factors of wheezing disorders, ethnic differences)	C. Kuehni, M. Silverman
18	AMICS-PAULA, 1999, Munich (Germany)	Asthma Multicentre Infant Cohort Study-Perinatal Asthma Environment Long-Term Allergy Study		553	A, AR, E (risk factors, genotypes)	E. von Mutius
19	KOALA, 2001, South, Central, West (The Netherlands)	Kind, Ouder en gezondheid, Aandacht voor Leefstijl en Aanleg (Child, Parents and Health: Lifestyle and Genetic Constitution)	16, 17, 45–47	2,834	A, AR, E, food allergies, sensitization, obesity (environmental, lifestyle, genetic factors)	C. Thijs

Table 2 (continued)

	Study acronym, start, setting	Study name	References	Recruited children, n	Main objectives	Principal investigators
20	VGB, 2003, Gothenburg, Western Gothia county (Sweden)	Vastra Gotaland Barn (Western Gothia Children) Study	48, 49	4,921	A, AR, E (natural course, risk factors)	G. Wennergren, B. Alm
21	GEPSII, 2003, Rome (Italy)	Gene and Environment Prospective Study on Infancy in Italy	50	708	A, AR, E, food allergies, obesity, neurodevelopmental disorders (risk factors, genotypes)	F. Forastiere
22	PARIS, 2003, Paris (France)	Pollution and Asthma Risk: an Infant Study	51, 52	3,855	A, AR, E occurrence of respiratory and allergic disorders in children (lifestyle, indoor, outdoor environment)	I. Momas
23	CO.N.ER, 2004, Bologna (Italy)	Coorte di Neonati in Emilia-Romagna	50	700	A, AR, E, food allergies, obesity, neurodevelopmental disorders (risk factors, genotypes)	M.P. Fantini
24	PLANK, 2004, Kaunas (Lithuania)	Pirmoji Lietuvos Alergijos Naujagimiu Kohorta (First Lithuanian Allergy Birth Cohort)	53, 54	205	A, AR, E (environmental factors)	R. Dubakiene
25	ALADDIN, 2004, Järna, near Stockholm (Sweden)	Assessment of Lifestyle and Allergic Disease During INfancy	49	330	A, AR, E, food allergies (environmental and particularly anthroposophic lifestyle factors)	J. Alm

Additional children were recruited older than 1 year of age. A = Asthma; R = rhinitis; AR = allergic rhinitis; E = eczema.

formed by J. Heinrich's working group (Helmholtz Zentrum, Munich) showed that exposure to visible mold and/or dampness (assessed by parental questionnaires) during the first 2 years of life was associated with an increased risk of developing asthma symptoms between 0 and 2 years [57]. Furthermore, active and passive smoking during pregnancy and the postnatal period was evaluated as a risk factor of childhood wheeze and asthma led by M. Wickman (Karolinska, Stockholm) and M. Kogevinas (CREAL, Barcelona). Corresponding manuscripts with the results are being prepared for publication [Neuman et al., in revision; Vardavas et al., in preparation].

CHICOS (FP7) 2010–2012

Goals and Methods

Many of the birth cohorts which participated in GA[2]LEN and ENRIECO are part of CHICOS (Developing a Child Cohort Research Strategy for Europe) and will perform further combined data analyses (e.g. meta-analyses) on potential risk factors for asthma and wheezing in young children including birth weight, catch-up growth, maternal complications in pregnancy, and mode of delivery. The overall aim of CHICOS is to develop an integrated strategy for mother-child cohort research in Europe and to make recommendations for research action at the European level for the next 15 years. The focus is on the wide determinants of child health (including allergy and asthma) and on how new knowledge from cohort studies can contribute to the best public health measures in terms of lifestyle, work and living circumstances.

CHICOS will review the information available in the European cohorts on child health determinants at the individual and community level (e.g. relating to socioeconomic factors and cultural contexts, diet and physical activity, tobacco, alcohol and other substances, and environmental factors). This will be achieved through the collaboration of important European mother-child cohorts including a searchable web-based inventory of these cohorts (http://www.birthcohorts.net).

Results

CHICOS has recruited 76 birth cohorts from 21 countries with a wide range of aims, and an inventory is being developed (http://www.birthcohorts.net). Many of the asthma and allergy birth cohorts which participated in GA[2]LEN and ENRIECO are part of CHICOS and will

perform further combined data analyses on the potential risk factors for respiratory diseases including the effects of fetal growth patterns and of mode of delivery on wheezing and asthma. So far, CHICOS has been able to take advantage of previous comparisons between centralized and decentralized analyses in ENRIECO and determine how to better develop an integrated strategy for mother-child cohort research in Europe which secures a more effective translation of scientific knowledge into public policies.

MeDALL (FP7) 2011–2014

MeDALL

The origin of the epidemic of IgE-associated (allergic) diseases is unclear. The project Mechanisms of the Development of ALLergy (MeDALL) [58], an FP7 project, aims to generate novel knowledge on the mechanisms of initiation of allergy and to propose early diagnosis, prevention, and targets for therapy. A novel phenotype definition and an integrative translational approach are needed to understand how a network of molecular and environmental factors can lead to complex allergic diseases. A novel, stepwise, large-scale, and integrative approach will be led by a network of complementary experts in allergy, epidemiology, allergen biochemistry, immunology, molecular biology, epigenetics, functional genomics, bioinformatics, and computational and systems biology.

Goals and Methods of the MeDALL Birth Cohort Study

Within MeDALL, several of the older and younger European birth cohorts on asthma and allergy which previously collaborated in GA^{2}LEN and ENRIECO are performing a harmonized follow-up assessment with identical questionnaires and clinical methods. Their study participants will be in preschool and early school age (4–10 years) and in adolescence (14–18 years) (table 3). Previously collected (historical) data and new follow-up data using a harmonized questionnaire will be included in a common database in order to perform pooled pan-European data analyses. The primary aims of these analyses will be the examination of early childhood predictors for allergy and asthma later in life as well as gender differences in the natural course of the disease. Unsupervised statistical analysis will be carried out to compare novel phenotypes (data-driven) to classical phenotypes (hypothesis-driven) [59].

Results

The following studies have been completed:

- Definitions of the classical phenotypes of allergic diseases were based on an initial literature review and agreed upon by experts in a MeDALL meeting organized in June 2011. A protocol for the review of classical phenotypes was drafted and an initial literature mining has been performed including 219 original studies and 129 ad hoc studies. This protocol can be valuable and applicable to systematic reviews for other complex and convoluted chronic diseases and has been submitted for publication.

- A harmonized questionnaire for prospective birth cohorts has been designed and is available as a web-based version in 4 different languages. This questionnaire will allow the comparison of prospective data across all participating birth cohorts.

- A pooled database of recent ongoing longitudinal birth cohorts on allergy-related phenotypes (atopic dermatitis, rhinitis, and asthma) has been built. It is using historical data from the 14 birth cohorts participating in MeDALL (table 3), which are spread across Europe, making this study unique in terms of geographical variability. The data of over 44,000 children have been included: 22,417 aged around 4–6 years and 18,975 aged around 8–10 years.

- Based on the pooled database, the prevalence of the classical phenotypes of allergic diseases using the MeDALL-agreed definitions was analyzed per age period (4–6 years, 8–10 years) in the pooled data and also per cohort, and according to the availability of specific antibodies against allergens in serum samples.

- An increasingly popular approach consists of applying unsupervised statistical methods to a population with a wide distribution of related symptoms and letting the statistical technique identify the possible underlying phenotypes. Each of these phenotypes should be as homogeneous as possible and have as little overlap as possible with each of the other phenotypes. These phenotypes (groups) are not known a priori, a problem known as unsupervised classification. These studies typically begin with no predefined views about the existing phenotypes and apply unsupervised statistical methods like cluster analysis [59]. The identification of novel phenotypes was based on cluster analysis using k means. One hundred and twenty-six cluster analyses were performed. Slight differences between complete cases and imputed were identified, as well as for clusters with and without IgE.

Table 3. European birth cohorts on asthma and allergy participating in MeDALL

	Study acronym, start, setting	Study name	References	Recruited children, n	Main objectives	Principal investigators
3*	MAS, 1990, Berlin, Düsseldorf, Mainz, Freiburg, Munich (Germany)	Multi-centre Allergy Study	18–21	1,314	A, AR, E, sensitization (natural course, risk factors)	T. Keil, S. Lau, U. Wahn
5*	ECA, 1992, Oslo (Norway)	Environment and Childhood Asthma	25–28	3,754	A, AR, E (environmental factors)	K.C.L. Carlsen, K.H. Carlsen
7*	BAMSE, 1994, Stockholm (Sweden)	Barn, Allergi, Miljo, Stockholm, en Epidemiologisk studie	31–34	4,089	A, AR, E (environmental factors)	M. Wickman
9*	PIAMA-NHS, 1996, North, Central, West (The Netherlands)	The Prevention and Incidence of Asthma and Mite Allergy-Natural History Study	37–39	3,291	A, respiratory allergies (incidence, risk factors)	H.A. Smit, B. Brunekreef
10*	GINI-Plus, 1996, Munich, Wesel (Germany)	German Infant Nutritional Intervention Study (observational part)	40	5,591	A, AR, E, food allergies (natural course, environmental and other risk factors)	J. Heinrich, U. Krämer, A. von Berg
12*	AMICS-Menorca, 1997, Island of Menorca (Spain)	Asthma Multicentre Infant Cohort Study-Menorca	29, 30	485	A, AR, E (environmental factors)	M. Torrent
13*	LISA, 1997, Leipzig, Munich, Wesel, Bad Honnef (Germany)	Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood	41	3,097	A, AR, E, food allergies, sensitization (natural course, risk factors, East vs. West Germany)	J. Heinrich
16*	DARC Study, 1998, Odense and surroundings (Denmark)	Danish Allergy Research Centre study	44	562	A, AR, E, food allergies (incidence, prevalence, risk factors)	C. Bindslev-Jensen
22*	PARIS, 2003, Paris (France)	Pollution and Asthma Risk: an Infant Study	51, 52	3,855	A, AR, E, occurrence of respiratory and allergic disorders in children (lifestyle, indoor and outdoor environments)	I. Momas
23*	ROBBIC, 2004**, Rome, Bologna (Italy)	Roma-Bologna birth cohort	50, 60	1,363	A, AR, E, food allergies, obesity, neurodevelopmental disorders (risk factors, genotypes)	D. Porta, M.P. Fantini, F. Forastiere
New	BIB, Bradford (UK)	Born in Bradford	61	13,776	Childhood obesity, developmental origins of adult disease, ethnicity, A, atopy	J. Wright
New	EDEN (France)	Etude des determinants pré et post natals du développement et de la santé de l'enfant	62	1,890	A, AR, indoor and outdoor environments on asthma and allergy	I. Annesi-Maesano
New	INMA (Spain)	INfancia y Medio Ambiente (Environment and Childhood) Project	63	2,021	Metabolic characteristics and neurodevelopmental disorders in children, early life risk factors (lifestyle, indoor, outdoor environment, genetics), A	J. Sunyer
New	RHEA, Heraklion (Greece)	Mother-child cohort in Crete	64	1,497	A, AR, E, obesity, cardio-metabolic characteristics, and neurodevelopmental disorders in children, early life risk factors (lifestyle, indoor, outdoor environment, genetics)	L. Chatzi

A = Asthma; R = rhinitis; AR = allergic rhinitis; E = eczema.
* Pooled in GA^{2}LEN (see table 1). ** ROBBIC is the association of the GASPII and CO.N.ER cohorts.

Future Needs and Potentials of Pooling Birth Cohorts on Allergy and Asthma

In this review, we have presented the main characteristics of four EU FP6–7-funded birth cohort initiatives; two of these focused on asthma and allergy and the other two on broader aims but also including asthma and allergy. Though two of these initiatives, CHICOS and MeDALL, are still in process and accumulating experience, additional networking efforts are needed. These efforts should focus on a set of strategic issues including:

- Reducing and, if possible, preventing fragmentation from one birth cohort study to another by favoring the development of sustainable networking capacities.
- Reducing the workload and economic cost of current one-by-one harmonization efforts.
- Improving our understanding of the pros and cons of centralized and decentralized approaches of combined birth cohort data analysis.
- Strengthening the capacity of developing harmonized research protocols and multilingual instruments.
- Developing bioinformatic infrastructures to facilitate flexible and transparent flows of data and samples across institutions with full respect to the ethics and propriety rules.

The pooling of birth cohorts in Europe under FP6 and FP7 has already led to significant results on asthma and allergy. Regarding MeDALL, it appears to be of importance to extend the inventory of existing birth cohorts with relevant information on asthma and allergy (http://www.birthcohorts.net) and to increase the number of birth cohorts included in the MeDALL database worldwide to make a unique study of a very large number of children followed from birth to the three important age groups: preschool children, 8–10 years, and 14–18 years. These efforts would enable a highly cost-effective strategy in order:

- To promote and facilitate the harmonization of existing questionnaires and clinical data of ongoing birth cohorts (for current and future studies).
- To propose future common questionnaires for different age groups and a common clinical study protocol to be used in new birth cohorts as well as in new follow-ups of ongoing birth cohorts, which could then be fully interoperable and facilitate better comparison with historical data already obtained.
- To analyze pooled data from ongoing birth cohort studies in large databases to complement newly developed birth cohorts.

- To increase the opportunities for mechanistic studies of existing and new samples (e.g. molecular sensitization profiles as determined by allergen chip technology) from prospectively designed long-term cohorts, which collected questionnaire and clinical data since birth and, in many cases, since pregnancy.

Appendix

MeDALL Study Group
J. Bousquet, J.M. Anto, M. Akdis, C. Auffray, T. Keil, D.S. Postma, R. Valenta, T. Haahtela, A. Cambon-Thomsen, B.N. Lambrecht, J. Sunyer, C.A. Akdis, I. Annesi-Maesano, A. Arno, C. Bachert, F. Ballester, X. Basagana, U. Baumgartner, C. Bindslev-Jensen, B. Brunekreef, K.H. Carlsen, L. Chatzi, E. Eller, F. Forastiere, J. Garcia-Aymerich, S. Guerra, U. Gehring, H. Hammad, J. Heinrich, C. Hohmann, F. Kauffmann, M. Kerkhof, M. Kogevinas, G.H. Koppelman, M.L. Kowalski, I. Kull, S. Lau, K.C. Lodrup-Carlsen, C. Lupinek, D. Maier, M.J. Makela, F.D. Martinez, I. Momas, M.C. Nawijn, A. Neubauer, S. Oddie, S. Palkonen, S. Reitamo, E. Rial-Sebbag, M. Salapatas, V. Siroux, D. Smagghe, H.A. Smit, M. Torrent, E. Toskala, A.J.M. van Oosterhout, R. Varaso, L. von Hertzen, M. Wickman, C. Wijmenga, and J. Wright.

GA[2]LEN Study Group
T. Zuberbier, J. Bousquet, P.G. Burney, P. Van Cauwenberge, C.A. Akdis, C. Bindslev-Jensen, S. Bonini, W.J. Fokkens, F. Kauffmann, T. Keil, M.L. Kowalski, U. Kramer, I. Kull, S. Lau, K. Lodrup-Carlsen, J. Mullol, E. Nizankowska-Mogilnicka, N. Papadopoulos, E. Toskala, M. Wickman, J. Anto, B. Alm, J. Alm, S.H. Arshad, C. Bachert, P.J. Bousquet, F. Bravi, B. Brunekreef, G.W. Canonica, K.H. Carlsen, A. Custovic, R. Dubakiene, E. Eller, M.P. Fantini, F. Forastiere, M. Gjomarkaj, S. Halken, A. Host, J. Heinrich, P. Howarth, C. Kuehni, J. Lotvall, I. Momas, M. Mommers, D. Porta, K. Radon, J. Ring, G. Roberts, M. Salapatas, H.J. Schünemann, A. Simpson, H.A. Smit, J. Sunyer, A. Szczecklik, C. Thijs, A. Todo-Bom, M. Torrent, R. Valenta, E. Valovirta, K. van Steen, A. Von Berg, E. von Mutius, U. Wahn, G. Wennergren, A.H. Wijga, and J.P. Zock.

CHICOS Study Group

M. Vrijheid, L. Chatzi, L. Duijts, V. Jaddoe, M. Kogevinas, D. Lawlor, P. Lucas, P. Magnus, F. Merletti, M. Nieuwenhuijsen, A.M. Nybo Andersen, H. Raat, C. Stoltenberg, and J. Sunyer.

ENRIECO Study Group

M. Nieuwenhuijsen, M. Vrijheid, M. Casas, A. Bergström, A. Carmichael, C.-M. Chen, S. Cordier, M. Eggesbø, E. Eller, M.P. Fantini, M.F. Fernández, A. Fernández-Somoano, U. Gehring, R. Grazuleviciene, J. Heinrich, C. Hohmann, A.M. Karvonen, T. Keil, M. Kogevinas, G. Koppen, U. Krämer, C.E. Kuehni, P. Magnus, R. Majewska, A.M. Nybo Andersen, E. Patelarou, M. Skaalum Petersen, F.H. Pierik, K. Polanska, D. Porta, L. Richiardi, A.C. Santos, R. Slama, R.J. Sram, C. Thijs, C. Tischer, G. Toft, T. Trnovec, S. Vandentorren, C. Vardavas, T.G.M. Vrijkotte, M. Wilhelm, and J. Wright.

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