Unique collaboration of European birth cohort studies on asthma and allergy in the GA²LEN network

Thomas Keil1, Magnus Wickman2,3, Inger Kull3,4, Karin C. Lødrup Carlsen5, Kai Håkon Carlsen6, Henriette A. Smit7, Alet H. Wijga8, Bert Brunekreef8,9, Andrea von Berg10, Ursula Krämer11, Esben Eller12, Carsten Bindslev-Jensen12, Susanne Halken13, Arne Høst13, Joachim Heinrich14, Maria Pia Fantini15, Francesca Bravi16, Daniela Porta16, Francesco Forastiere16, Monique Mommers17, Carel Thijs17, Jordi Sunyer18, Matias Torrent19, Graham Roberts20, Claudia Kuehni21, Ruta Dubakiene22, Göran Wennergren23, Bernt Alm2, Angela Simpson24, Adnan Custovic24, Ulrich Wahn25, Susanne Lau25, for the GA²LEN WP 1.5 work group26

1 Institute for Social Medicine, Epidemiology and Health Economics, Charité, Berlin, Germany
2 Sachs’ Children’s Hospital, Stockholm, Sweden
3 National Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
4 Dept. of Occupational and Environmental Health, Stockholm County Council, Stockholm, Sweden
5 Dept. of Pediatrics, Ullevål University Hospital, Oslo, Norway
6 Voksentoppen BKL, National Hospital of Norway HF, Oslo, Norway
7 National Institute for Public Health and the Environment, Bilthoven, The Netherlands
8 Institute for Risk Assessment Sciences, Utrecht University, The Netherlands
9 Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands
10 Dept. for Pediatrics, Marien-Hospital, Wesel, Germany
11 IUF - Institut für Umweltmedizinische Forschung, Düsseldorf, Germany
12 Allergy Center, Dept. of Dermatology, Odense University Hospital, Denmark
13 Dept. of Paediatrics, Odense University Hospital, Denmark
14 Institute of Epidemiology, GSF, Neuherberg, Germany
15 Dept. of Public Health, Alma Mater Studiorum, University of Bologna, Italy
16 Dipartimento di Epidemiologia ASL Rim E, Rome, Italy
17 School for Public Health and Primary Care, and Nutrition and Toxicology Research Institute Maastricht (NUTRIM), Dept. of Epidemiology, Maastricht University, The Netherlands
18 Environmental Epidemiology Research Centre (CREAL), Institut Municipal d'Investigacio Medica (IMIM), Barcelona, Spain
19 Menorca Health Area, ib-salut, Menorca, Spain
20 Paediatric Allergy and Respiratory Medicine, University Child Health, Southampton University Hospital, UK
21 Institute of Social and Preventive Medicine, University of Bern, Switzerland
22 Allergy Centre, Vilnius University, Lithuania
23 Dept. of Paediatrics, Gothenburg University, Sweden
24 University of Manchester, North West Lung Centre, Wythenshawe Hospital, Manchester, UK
25 Dept. for Paediatric Pneumology and Immunology, Allergy Centre Charité, Berlin, Germany
26 Global Allergy and Asthma European Network (GA²LEN) - Work Package 1.5 “Birth Cohorts”

Correspondence: T. Keil, thomas.keil@charite.de

Refer to this paper as:
Abstract
Background and aim: Longitudinal studies particularly birth cohort studies are needed to examine risk or protective factors for asthma and allergy. Within the Global Allergy and Asthma European Network (GA²LEN) one of the work packages was designed to identify and compare ongoing European birth cohort studies on asthma and allergic diseases.

Methods and results: We established a database of relevant characteristics of 24 observational birth cohort studies designed to examine asthma and allergies in 9 European countries. For subjective assessment of asthma and allergic rhinitis most birth cohorts applied ISAAC questions, whereas the definition of eczema was not as homogeneous across the studies. Several cohorts performed lung function tests, but no comparable standard procedures were used. Data on sensitisation to various inhalant and food allergens was assessed by specific IgE in 17 studies, by skin prick tests in 12 studies. Using blood or buccal samples most studies extracted DNA (or intend to do so) for genetic analyses.

Conclusion and outlook: Due to the unique cooperation within the GA²LEN network a common database was established containing characteristics of 24 European birth cohort studies on asthma and allergic diseases. After defining comparable categories across the different cohorts 12 study teams are currently pooling data for specific research questions. This will result in statistically powerful analyses with data from over 20,000 European children. Furthermore, the collaborating birth cohorts will attempt to harmonise their assessments methods.

Study names of European birth cohorts examining asthma and allergic diseases:

1. ALADDIN – Assessment of Lifestyle and Allergic Disease During INfancy (Sweden)
2. AMICS-Ashford – Asthma Multicentre Infant Cohort Study-Ashford (UK)
3. AMICS-Barcelona – Asthma Multicentre Infant Cohort Study-Barcelona (Spain)
4. AMICS-Menorca – Asthma Multicentre Infant Cohort Study-Menorca (Spain)
5. AMICS-PAULA – Asthma Multicentre Infant Cohort Study-Perinatal Asthma Environment Longterm Allergy-Study (Germany)
6. Amnio-Study (UK)
7. BAMSE – Barn Allergi Miljö Stockholm Epidemiologi Projektet (Sweden)
8. CO.N.ER – Coorte di Neonati in Emilia-Romagna (Italy)
9. DARC-Study – Danish Allergy Research Centre study (Denmark)
10. ECA – Environment and Childhood Asthma (Norway)
11. GEPSII – Gene and Environment Prospective Study on Infancy in Italy (Italy)
12. GINI-B – German Infant Nutritional Intervention-Study [observational part] (Germany)
13. Isle of Wight Study (UK)
14. KOALA – Kind, Ouder en gezondheid, Aandacht voor Leefstijl en Aanleg [Child, Parents and Health: Lifestyle and Genetic Constitution] (The Netherlands)
15. Leicester 1990 Cohort (UK)
16. Leicester 1998 Cohort (UK)
17. LISA – Influences of Lifestyle-related Factors on the Immune-system and the development of allergies in childhood (Germany)
18. MAAS – Manchester Asthma and Allergy Study (UK)
19. MAS – Multi-centre Allergy Study (Germany)
20. Odense 1985 (Denmark)
21. PIAMA-NHS – The Prevention and Incidence of Asthma and Mite Allergy -Natural History Study (The Netherlands)
22. PLANK – Pirmoji Lietuvos Alergijos Naujagimiu Kohorta [First Lithuanian Allergy Birth Cohort] (Lithuania)
23. **SEATON** – Study of Eczema and Asthma To Observe the influence of Nutrition (UK)
24. **VGB** – Västra Götaland Barn [Western Gothia Children] Study (Sweden)
Background
It remains unclear why the prevalence of asthma and allergic diseases has increased steadily, particularly in the western world. Lifestyle factors, environmental exposures and/or interactions between genes and the environment most likely play a causal role. In order to detect cause-effect relationships it is essential to carry out longitudinal epidemiological studies. For diseases that can start as early as in infancy, a birth cohort study is the best possible study design.

One of the work packages within the Global Allergy and Asthma European Network (GA²LEN) (1, 2) was designed to identify all European birth cohorts on asthma and allergic diseases, to create a common database of the different study characteristics, allowing the comparison of study methods and evaluating the possibility to pool data and perform common analyses, furthermore, to recommend criteria for conducting future birth cohorts or follow-up assessments of existing cohorts.

The present report gives an overview of the common database of currently 24 European birth cohorts on asthma and allergic diseases comparing study design, study setting, target population, recruitment criteria, follow-up rates, assessment of objective and subjective outcome parameters as well as of relevant exposure parameters.

Methods
We created a common database for relevant study characteristics of European observational birth cohort studies on asthma and allergic diseases as described in detail elsewhere (3, 4). The structure of the existing database allows to enter further information for existing as well as for new birth cohorts. The term ‘cohort study’ was used according to epidemiological and evidence-based medicine criteria strictly for observational studies (5).

Intervention studies (randomised or clinically controlled trials) of newborns or of pregnant mothers investigating preventive measures, such as hypoallergenic formula or dust mite impermeable mattress covers, were excluded. Some researchers recruited participants for both observational and intervention studies. For the purposes of this database, only the observational arms of the studies were included. All studies were included regardless of sample size or whether the data had been analysed or published. Cross-sectional studies were excluded, since a causal relationship cannot be established with this study design.

Results
By September 2007, we collected characteristics of 24 observational birth cohort studies (from 9 European countries) designed to examine asthma and allergic disease, with a total of over 40,000 recruited children. Most of the birth cohorts have been initiated in Northern and Western Europe. During the last 10 years the first birth cohort studies in Southern (Spain, Italy) and Eastern (Lithuania) Europe started (Table 1).

Study design
Seven large studies in Norway (ECA), Sweden (BAMSE, VGB), The Netherlands (PIAMA-NHS, KOALA), Germany (LISA, GINI-B) and UK (Leicester 1998) have recruited around 3000 or more participants each. Almost all studies are investigating primarily asthma, allergic rhinitis and eczema as main outcomes, 9 cohorts have an additional focus on food allergies. The examination of environmental factors was emphasised by 11 studies (Table 1). In general, the study settings were in urban, particularly metropolitan areas. Seven birth cohorts included also children from mixed urban/rural backgrounds: the Dutch PIAMA-NHS and KOALA, the German GINI-B, the 2 Leicester cohorts (UK), the Swedish VGB and
ALADDIN. Only the 2 island-based studies (Isle of Wight, UK, and AMICS-Menorca, Spain) have rural settings. The majority of the birth cohorts recruited their children in university/academic teaching hospitals. Few chose health care centres, family/prenatal care medical practices, mid-wife practices or population registries (Table 1).
Table 1: European birth cohort studies designed to examine asthma and allergic diseases.

<table>
<thead>
<tr>
<th>Study Acronym, Start, Setting</th>
<th>Main objectives A=asthma, AR=allergic rhinitis, E=eczema</th>
<th>Recruited children (n)</th>
<th>Recruitment location</th>
<th>Principal investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 Odense 1985, Odense (Denmark)</strong></td>
<td>A, AR, E, food allergies, sensitisation. (natural course; risk factors)</td>
<td>276</td>
<td>University hospital</td>
<td>A. Høst, S. Halken</td>
</tr>
<tr>
<td><strong>2 Isle of Wight, 1989, Isle of Wight (UK)</strong></td>
<td>A, E, food allergies (environmental factors)</td>
<td>1456</td>
<td>Antenatal clinic</td>
<td>H. Arshad, G. Roberts</td>
</tr>
<tr>
<td><strong>3 MAS, 1990, Berlin, Düsseldorf, Mainz, Freiburg, Munich (Germany)</strong></td>
<td>A, AR, E, sensitisation (natural course; risk factors)</td>
<td>1314</td>
<td>6 university hospitals</td>
<td>U. Wahn, S. Lau</td>
</tr>
<tr>
<td><strong>4 Leicester 1990 Cohort, Leicester, Leicestershire County (UK)</strong></td>
<td>A (natural course, risk factors of wheezing disorders)</td>
<td>570*</td>
<td>Health Authority, Child Health Database</td>
<td>C. Kuehni, M. Silverman</td>
</tr>
<tr>
<td><strong>5 ECA, 1992, Oslo (Norway)</strong></td>
<td>A, AR, E (environmental factors)</td>
<td>3754</td>
<td>2 main hospitals (90% of all deliveries)</td>
<td>K.C. L. Carlsen, K.H. Carlsen</td>
</tr>
<tr>
<td><strong>6 AMICS-Ashford, 1993, Ashford, Kent (UK)</strong></td>
<td>A, AR, E (environmental factors)</td>
<td>642</td>
<td>3 family medical practices</td>
<td>P. Cullinan</td>
</tr>
<tr>
<td><strong>7 BAMSE, 1994, Stockholm (Sweden)</strong></td>
<td>A, AR, E (environmental factors)</td>
<td>4089</td>
<td>58 health care centers in 4 districts</td>
<td>M. Wickman</td>
</tr>
<tr>
<td><strong>8 MAAS, 1995, Manchester (UK)</strong></td>
<td>A, AR, E (environmental factors)</td>
<td>957</td>
<td>Antenatal clinics in 2 hospitals</td>
<td>A. Woodcock, A. Custovic</td>
</tr>
<tr>
<td><strong>9 PIAMA-NHS, 1996, North, Central, West (The Netherlands)</strong></td>
<td>A, respiratory allergies (incidence; risk factors)</td>
<td>3291</td>
<td>52 mid-wives practices (incl. 12 in Rotterdam)</td>
<td>H.A. Smit, B. Brunekreef</td>
</tr>
<tr>
<td><strong>10 GINI-B, 1996, Munich and Wesel (Germany)</strong></td>
<td>A, AR, E, food allergies (natural course; environmental and other risk factors)</td>
<td>3739</td>
<td>Munich: 8 hospitals (incl. 2 university) Wesel: 7 hospitals</td>
<td>U. Krämer, A. von Berg</td>
</tr>
<tr>
<td><strong>11 AMICS-Barcelona, 1996, Barcelona (Spain)</strong></td>
<td>A, AR, E (environmental factors)</td>
<td>487</td>
<td>District hospital</td>
<td>J. Sunyer</td>
</tr>
<tr>
<td><strong>12 AMICS-Menorca, 1997, Island of Menorca (Spain)</strong></td>
<td>A, AR, E (environmental factors)</td>
<td>485</td>
<td>All prenatal care general practices</td>
<td>M. Torrent</td>
</tr>
<tr>
<td><strong>14 SEATON, 1997, Aberdeen (UK)</strong></td>
<td>A, AR, E (diet)</td>
<td>1924</td>
<td>Antenatal clinic in 1 hospital</td>
<td>A. Seaton, G. Devereux</td>
</tr>
<tr>
<td><strong>16 DARC-Study, 1998, Odense and surroundings (Denmark)</strong></td>
<td>A, AR, E, food allergies (incidence, prevalence, risk factors)</td>
<td>562</td>
<td>University hospital</td>
<td>C. Bindslev-Jensen</td>
</tr>
<tr>
<td><strong>17 Leicester 1998 Cohort, Leicester (UK)</strong></td>
<td>A (natural course, risk factors of wheezing disorders; ethnic differences)</td>
<td>4247*</td>
<td>Health Authority, Child Health Database</td>
<td>C. Kuehni, M. Silverman</td>
</tr>
<tr>
<td><strong>18 AMICS-PAULA, 1999, Munich (Germany)</strong></td>
<td>A, AR, E (risk factors, genotypes)</td>
<td>553</td>
<td>Academic teaching hospital</td>
<td>E. von Mutius</td>
</tr>
<tr>
<td><strong>19 KOALA, 2001, South, Central, West (The Netherlands)</strong></td>
<td>A, AR, E, food allergies, sensitisation, obesity (environmental, lifestyle, genetic factors)</td>
<td>2834</td>
<td>Mid-wife practices and hospitals</td>
<td>C. Thijss</td>
</tr>
<tr>
<td><strong>20 VGB, 2003, Gothenburg and Western Gotia county (Sweden)</strong></td>
<td>A, AR, E (natural course, risk factors)</td>
<td>4921</td>
<td>Health Authority, Child Register</td>
<td>G. Wennergren, B. Alm</td>
</tr>
<tr>
<td><strong>21 GEPSII, 2003, Rome (Italy)</strong></td>
<td>A, AR, E, food allergies, obesity, neurodevelopmental disorders (risk factors, genotypes)</td>
<td>708</td>
<td>2 large hospitals</td>
<td>F. Forastiere</td>
</tr>
<tr>
<td><strong>22 CO.N.E.R, 2004, Bologna (Italy)</strong></td>
<td>A, AR, E, food allergies, obesity, neurodevelopmental disorders (risk factors, genotypes)</td>
<td>700</td>
<td>1 large hospital</td>
<td>M.P. Fantini</td>
</tr>
<tr>
<td><strong>23 PLANK, 2004, Kaunas (Lithuania)</strong></td>
<td>A, AR, E (environmental factors)</td>
<td>205</td>
<td>1 large hospital</td>
<td>R. Dubakiene</td>
</tr>
<tr>
<td><strong>24 ALADDIN, 2004, Järna, near Stockholm (Sweden)</strong></td>
<td>A, AR, E, food allergies (environmental and particularly anthroposophic lifestyle factors)</td>
<td>330</td>
<td>Anthroposophic and conventional maternity welfare centres</td>
<td>J. Alm</td>
</tr>
</tbody>
</table>

* additional children were recruited at age 2 and older
Objective outcome parameters

Sensitisation assessed by Immunoglobulin E (IgE)

Cord blood was collected in 14 of the 24 birth cohorts (from over 11,000 children) to perform IgE measurements as well as further analyses, such as specific IgG or CD14. Seventeen studies investigated the development of sensitisation assessed by specific serum IgE to various aero- and food allergens: mite, cat, dog, grass, birch, milk and egg; some studies additionally to moulds, peanut, wheat, soy, fish (cod, trout), horse and/or cockroach. BAMSE (Sweden), GINI-B and LISA (both Germany) collected the largest number of IgE data, each from >2000 children.

Sensitisation assessed by skin prick test (SPT)

Twelve birth cohorts performed SPT. Up to age 10 years there is data available for a total number of children ranging from 1100 to >2500 per year. Using SPT solutions of different companies, most studies tested for grass and tree pollen, mite, cat, dog, milk and egg allergens, while other allergens (such as from other foods) were considered less frequently.

Lung function tests

Eleven birth cohorts assessed lung function in their study children, some only in subgroups of the total study population. There is only little data in very young children reflecting the fact that children of this age often cannot perform forced expiratory manoeuvres reliably. However, the ECA study (Norway) did lung function tests (e.g. tidal flow volume in the awake state) in over 800 newborns, of whom 614 were re-examined at 10 years of age. Across the studies and age groups there was no standard procedure of measuring lung function. Mostly spirometry was performed (although with many different devices across the studies), sometimes also as part of a bronchial challenge test which was used to determine bronchial hyperresponsiveness to either cold/dry air, methacholine, histamine, or exercise. A few studies tested reversibility by the application of bronchodilators, but using different substances. Furthermore, some birth cohort studies measured airway resistance using the interrupter technique (Rint), several others also examined exhaled NO.

Subjective outcome parameters

For the assessment of symptoms regarding asthma (wheezing) and allergic rhinitis, most birth cohorts used the standardised questions (sometimes modified) from the ISAAC questionnaire. To further assess allergic respiratory symptoms, almost all studies developed additional own questions. Some studies had an additional focus on possible allergic reactions to food. To assess eczema signs/symptoms most cohorts developed their own questions and/or used the ISAAC method.

Exposure variables

Across the studies a broad spectrum of exposure parameters was assessed (‘exposure’ in the epidemiological sense, meaning any objective and/or subjective factor that can potentially influence disease).

Biological factors

To examine possible genetic determinants of asthma or allergic diseases 14 birth cohorts collected blood, either at baseline or during follow up, to extract DNA (in some studies the extraction of DNA is pending). In some cases buccal swabs were collected for DNA
extraction with whole genome amplification. All studies combined, DNA is available from
almost 15 000 children.
Many studies stored serum and/or plasma for future measurements of inflammatory markers
or proteomic studies, some breast milk samples, and DARC (Denmark), and KOALA (NL)
collected faecal samples.

**Environmental and psychosocial factors**
During the first year of life, 11 studies collected dust samples to analyse exposure to mite or
pet allergens as a risk factor for sensitisation or allergic diseases. The methods for dust
sampling were not standardised across studies: samples were taken (i) from varying locations,
such as the children’s and/or parents’ mattress, bedroom and/or living room floor or the sofa;
(ii) by study team members or by parents; (iii) by supplied or by own devices; (iv) some
studies sieved the dust while others did not.
To varying degrees, all studies have collected subjective information regarding
socioeconomic status, passive smoking, pet exposure, day-care, siblings or breast feeding.
Some studies extensively assessed the home environment, e.g. by personal visits from
environmental inspectors or trained study team members and/or by detailed questionnaires. A
few studies collected detailed information on psychological factors, others used very detailed
questionnaires on dietary intake with measures of maternal vitamin levels, such as SEATON
(UK).

**Discussion**
The great interest of the participating European research teams to collaborate active support
encouraged us to plan and program a new database, enabling us to assess 24 birth cohorts so
far. This included all relevant characteristics regarding study design, objectives, potential
predictors and objective as well as subjective outcomes for asthma and allergic disease. Some
birth cohort studies are currently planning to pool data to perform common analyses.

**Objectives and recruitment of participants**
The included European birth cohort studies aimed to examine incidence, prevalence, natural
course and risk factors for asthma and allergic disease. Most study teams chose metropolitan
areas or major cities for their setting. Their incidence or prevalence estimates need to be
interpreted with caution, since asthma and respiratory allergies seem more common in urban
than in rural areas (6-8).
Several studies recruited children from university or academic teaching hospitals. This can be
regarded as representative for a particular city or region only, if the obstetric department is the
only one in the area and most of the local children are born there. On the other hand, in many
big cities in Germany different types of hospitals exist and obstetric departments of university
hospitals are more likely to admit a higher proportion of mothers with high risk
pregnancies/deliveries. Children recruited in academic teaching hospitals would differ from
children born in non-academic teaching hospitals and are probably not representative for the
general population.
Findings of a birth cohort study need to be interpreted carefully if the selection of participants
was linked to the recruitment process for an intervention study. Intervention studies on asthma
and allergy, e.g. to examine the efficacy of preventive measures, require children “at risk” for
allergies (parents with asthma/atopy). Families who are willing to participate in intervention
studies on allergic disease could differ from less interested families, regarding many factors:
higher risk for allergies, better motivation to follow a strict trial protocol, higher socioeconomic status or other factors. Birth cohorts recruiting families after an intervention study recruitment are at risk of selection bias by including less “high risk” children and less motivated parents than in the source population. To assess possible selection or initial non-response bias, it is important to determine whether the recruited study population differs from the source population.

Follow-up
The follow-up rates will presumably decrease in birth cohorts the longer the study periods are. Losses to follow-up occur due to various reasons, e.g. moves or migration, losing interest or refusing to participate, particularly in case of invasive diagnostic tests. Some investigators indicated that healthier children were more likely to drop-out of their studies. This can lead to an increasing percentage of allergic or “high-risk” children in the remaining cohort. Other investigators assumed that in their study especially allergic children seem to drop out faster because the study participation is perceived as another burden to the families in addition to already many doctor and hospital visits. However, low follow-up rates can threaten the generalisability and interpretation of the results, or reduce the statistical power of the analyses. Cohorts that were able to maintain high follow-up rates were more likely single-centre studies and/or had a study team that was highly successful in keeping contact with families and tracking down those who moved away.

Objective outcome parameters
Nineteen of the 24 birth cohorts objectively assessed sensitisation by measuring specific IgE and/or performing skin prick tests to various allergens. Specific IgE-tests to common allergens such as mite, cat, dog, grass, birch, milk and egg were measured in many studies at different time points during follow-up. For allergens that are less common causes of sensitisation, such as some food allergens, it could be of particular interest to combine data for common statistically more powerful analyses. A possible limiting factor for common analyses of specific IgE findings could be the lack of standardised laboratory methods, including heterogeneous allergen extracts. However, for IgE to pollen concordance of results in different assays seem to be satisfactory (9-11). Apart from the lack of validated standardised solutions there seems to be some heterogeneity with skin prick test methods although recommendations for the performance of skin prick testing exist (eg EAACI position papers). One recommendation for determining a positive skin prick test to an allergen is a mean wheal diameter ≥3 mm greater than the negative control. Other researchers prefer to use the skin index (allergen/histamine wheal ≥0.6) to determine a positive test. However, the number of positive results is influenced by the potency of the extract and the pressure applied on the prick lancet limiting the comparability of test results (12).

Twelve studies have objective data on (allergic) asthma or respiratory disease from lung function tests, but only few in preschool children. As methods (and devices) to assess lung function vary considerably, pooling data from different birth cohorts does not seem reasonable (13, 14).

Subjective outcome parameters
Many studies have assessed allergic rhinitis and asthma symptoms using standardised methods according to the ISAAC questionnaire. Therefore, selecting current (=last 12
months) wheezing or hay fever for common analyses of subjective outcome parameters could potentially include data from many of the GA²LEN birth cohorts.

**Exposure variables**
No standardised questions for family history of allergic diseases, pet ownership, socioeconomic status, tobacco smoke exposure, housing, day-care etc, were used. However, by some adaptations, it should be possible to examine potentially influential factors such as family history, pet ownership or tobacco smoke exposure in common data analyses. Regarding indoor allergens from dust samples, the different dust collection methods need to be considered. In order to minimise sampling device bias, Wickens et al. recommended that, allergen and endotoxin are expressed as a concentration, and that the bed is considered the major source of allergen exposure. In order to have confidence in comparisons of allergen and endotoxin reservoir levels between centres, standardisation in the use of sampling equipment is important (15, 16).

**Strengths and limitations**
Although we were able to identify 24 European birth cohort studies specifically designed to examine asthma and allergy, we may have missed studies which presently have not published any data or are still in the planning process. The effort of the GA²LEN - work package 1.5 “birth cohorts” is work in progress, and further research teams are encouraged to join this working group.

So far, the collaboration has been excellent between all participating European birth cohorts on asthma and allergic disease and a trustful basis has been created for common research activities in the future. Pooling data for meta-analyses would increase the statistical power and might allow the examination of less common exposures for asthma and allergic disease. A possible limitation to this approach is the non-standardised assessments of exposure and outcome variables between studies.

**Conclusions**
- An excellent pan-European collaboration has emerged between the participating research teams of the GA²LEN - work package 1.5 “birth cohorts”.
- It was possible to establish a common database of relevant characteristics of 24 European birth cohort studies.
- This unique initiative offers the opportunity to pool data and perform meta-analyses:
  - for selected *objective* outcome variables, such as sensitisation assessed by IgE
  - for selected *subjective* outcome variables, assessed by standardised questions on asthma, wheezing or allergic rhinitis according to the ISAAC protocol, or doctor-diagnosed asthma.
- Potential risk or protective factors (pet ownership, tobacco smoke exposure, day-care and others) were assessed comprehensively in most studies but not in a standardised way. It is necessary to define uniform categories.
- The ongoing birth cohort studies are harmonising future follow-up assessments to better examine and compare factors that can cause asthma and allergic diseases across Europe.
Acknowledgements
The study was supported by the Global Allergy and Asthma European Network (GA²LEN), a network of excellence (FOOD-CT-2004-506378), under the Sixth Framework Programme for Research of the EU. Collection of study characteristics from the UK studies was funded by Asthma UK. We express our special gratitude to all principal investigators and contributors of the 24 included birth cohorts. In particular, we would like to thank H. Arshad (Isle of Wight study, UK); P. Cullinan (AMICS, Ashford, UK); G. Devereux (SEATON, Aberdeen, UK); G. Faldella (CO.N.ER, Bologna, Italy); O. Herbarth (LISA, Leipzig, Germany); B. Schaaf (LISA, Bad Honnef, Germany); A. Seaton (SEATON, Aberdeen, UK); M. Silverman (Leicester 1990 and 1998 cohorts, UK); E. von Mutius (AMICS-PAULA, Munich, Germany); J. Warner (Amnio study, Southampton, UK); H.-E. Wichmann (GINI-B and LISA, Munich, Germany) and A. Woodcock (MAAS, Manchester, UK).

References
