

Original article

European birth cohort studies on asthma and atopic diseases:
I. Comparison of study designs – a GA²LEN initiative

Background: The reasons for the rise in asthma and allergies remain unclear. To identify risk or protective factors, it is essential to carry out longitudinal epidemiological studies, preferably birth cohort studies. In Europe, several birth cohort studies on asthma and atopic diseases have been initiated over the last two decades.

Aim: One of the work packages within the Global Allergy and Asthma European Network (GA²LEN) project was designed to identify and compare European birth cohorts on asthma and atopic diseases. The present review (part I) describes their objectives, study settings, recruitment process and follow-up rates. A subsequent review (part II) will compare outcome and exposure parameters.

Methods: For each birth cohort, we collected detailed information regarding recruitment process, study setting, baseline data (pregnancy, birth, parents/siblings) as well as follow-up rates, outcome and exposure parameters at each time point.

Results: We identified and assessed 18 European birth cohorts on asthma, allergic rhinitis and eczema. Six of these studies also focused on food allergies. The birth cohorts were mostly initiated in the 1990s with predominantly urban/metropolitan settings. Many studies were able to maintain high follow-up rates, even after five or more years.

Conclusions: Due to the unique cooperation within the GA²LEN project a common database was established containing study characteristics of European birth cohorts on asthma and atopic diseases. This can be used as a basis for evaluating the possibility to pool data and perform meta-analyses, as well as to recommend criteria for conducting future birth cohorts.

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Background

In the mid-1990s, the International Study of Asthma and Allergies in Childhood (ISAAC) collected data from children aged 13–14 years worldwide. In Europe, the 12-month prevalence for self-reported asthma ranged from 3% (Albania) to 32% (UK), for allergic rhinitis symptoms from 4% (Albania) to 19% (Ireland), and for eczema from 1% (Albania) to 19% (UK) (1). In addition to the high prevalence, particularly in industrialized countries, the socio-economic burden of asthma and allergies is enormous. In 1998, asthma in the USA accounted for an estimated 13 billion US dollars, mostly for direct medical expenditures (2). Based on Swedish data, an extrapolation was made for the major allergic diseases in Western Europe resulting in 10 billion EUR for direct costs and 19 billion EUR for indirect costs (3). Asthma is the leading cause of hospitalization of children and one of the main reasons for missing school.

The increasing prevalence of asthma and atopic diseases over the last decades cannot be explained by genetic susceptibility. Lifestyle factors, environmental exposures and/or interactions between genes and the environment most likely play a causal role.

The Global Allergy and Asthma European Network (GA²LEN) is a network of excellence selected by the European Commission. This consortium of 24 leading European research teams and two societies (European Academy of Allergy and Clinical Immunology, EAACI, and European Federation of Asthma and Allergy Associations, EFA) is committed to establish a research area of excellence in the field of allergy and asthma. A proposed grant of 14.4 million EUR for a period of 5 years will contribute towards linking scientific research centres throughout Europe. The aims are to harmonize diagnostic and therapeutic procedures, accelerate the application of research results to clinical practice, patients' needs and policy development, as well as to promote training and integration between public and private sectors (4).

One of the GA²LEN work packages was designed to identify and combine research activities between all European birth cohorts on asthma and atopic diseases. In order to detect cause–effect relationships it is essential to carry out longitudinal epidemiological studies. For diseases that occur from infancy, a birth cohort study is the best possible design. In Europe, several birth cohort studies on asthma and atopic diseases have been started over the last two decades, initially in Northern and Western, subsequently also in Southern European countries. A common database of the methods applied in these birth cohorts could be used as a basis for evaluating the possibility to pool data and perform meta-analyses as well as to recommend criteria for conducting future birth cohorts or follow-up assessments of existing cohorts.

The present review (part I) describes and compares primary objectives, study settings, recruitment process

and follow-up rates of European birth cohorts on asthma and atopic diseases. A subsequent review (part II) will compare outcome and exposure parameters relevant to allergic diseases.

Methods

Database

In preparation for setting up a common database, we reviewed the existing database of UK birth cohorts on asthma established by Simpson and Custovic (Manchester) for the Asthma UK Early Life Task Force. This database included study characteristics of birth cohorts from seven UK centres, focusing on early life predictors of asthma.

The intention of the GA²LEN initiative on birth cohorts was broader than the Asthma UK project and required programming a new database for collecting more detailed information on other related atopic diseases (allergic rhinitis and eczema) and on the recruitment process (to determine aspects of the generalizability of the birth cohorts).

Selection criteria

We included European birth cohort studies examining the prevalence, incidence, predictors and natural history of asthma and atopic diseases (allergic rhinitis, eczema, sensitization). The term 'cohort study' was used strictly for observational studies according to epidemiological and evidence-based medicine criteria (5). Intervention studies (randomized or nonrandomized trials) 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 purpose of this database, only the observational arms of these studies were included. All birth cohorts were considered regardless of sample size or whether the data had been analysed or published. Cross-sectional studies were excluded, as a causal relationship cannot be established with this study design.

Assessment of birth cohort studies

In long-term birth cohort studies (some ongoing for more than 10 years) where study personnel can change or different staff may be involved for different assessments, it can be difficult to obtain all information of interest. Therefore, all relevant study team members, such as project/subproject coordinators, study nurses, statisticians, etc. were visited on site and interviewed face to face. If necessary, the relevant parts of questionnaires were translated directly by a native speaker and databases checked for exact numbers of study participants or samples at each follow-up, for the total cohort and subgroups.

Study characteristics

The following basic study characteristics were assessed primarily:

- (i) primary/secondary study objectives
- (ii) study setting, recruitment period (first and last child included)
- (iii) source population, recruitment process, inclusion/exclusion criteria, number of eligible participants
- (iv) information on pregnancy, birth, collected/stored biological samples

- (v) for mother, father, siblings: asthma/atopic history, medication use, socio-demographic baseline data, collected/stored specimen, serum and skin tests
- (vi) details for communication of at least two contact persons from each birth cohort
- (vii) major and minor sponsors
- (viii) software for data management, data analysis.

In addition, for each year of follow-up we determined what type of information (and for how many children) the studies had collected regarding:

- (i) asthma, allergic rhinitis, eczema (validated questionnaires?)
- (ii) food and other allergies
- (iii) diet (validated or own questions)
- (iv) medication for asthma or atopic diseases
- (v) lung function
- (vi) skin tests
- (vii) immunoglobulin E tests
- (viii) collected/stored urine and/or serum
- (ix) dust samples
- (x) environment (including housing, animal contact)
- (xi) sibling(s)
- (xii) day-care/kindergarten/school
- (xiii) tobacco smoke exposure
- (xiv) parental socioeconomic status
- (xv) pet ownership
- (xvi) vaccinations
- (xvii) weight/height
- (xviii) additional other data.

Furthermore, for each follow-up assessment the database contains:

- (i) time points of follow-up (for the first 3 years in months, later in years)
- (ii) method of data collection (questionnaire, interview and/or physical examination)
- (iii) response rate
- (iv) use of incentives for parents or children to participate.

For each birth cohort study, the structure of the existing database allows for entry of further information for follow-up until 18 years of age.

Results

By February 2005, the GA²LEN-work package 'birth cohorts' had established a common database of all relevant study characteristics of 18 observational birth cohort studies designed to examine asthma and atopic disease. They came from eight European countries: the first (Denmark) and most of the subsequent birth cohorts have been initiated in Northern and Western Europe (UK, Germany, Norway, Sweden, the Netherlands). Since 1996 Southern European birth cohorts were initiated in Spain and, most recently, in Italy. We could not identify any birth cohort on asthma and atopic disease in Eastern Europe (Fig. 1).

Between 1992 and 1999, every year at least one new birth cohort started, seven in 1996/1997 alone. Five large studies from Norway, Sweden, the Netherlands and Germany have recruited over 3000 participants each. Of these large cohorts only the Dutch PIAMA-NHS has



Figure 1. European birth cohorts designed to examine asthma and atopic diseases: location of coordinating institutions.

been conducting annual follow-ups as have two smaller studies, the German MAS (up to 13 years by now) and AMICS-PAULA (5 years). Three studies provide extensive data from infancy and the year after: the German MAS and LISA as well as the Danish DARC-study assessed their children at six time points during the first 2 years of life (Fig. 2).

Furthermore, a contact was established with two large European pregnancy/birth cohort studies examining a broad spectrum of influential factors related to the health and development of fetus and child: the Avon Longitudinal Study of Parents and Children (ALSPAC) from Bristol, UK, which recruited 14 000 participants in 1991–1992, and the Danish National Birth Cohort Study with 100 000 participants recruited from 1997 to 2002 (6, 7). For these two cohorts we did not assess details of study design and outcomes in our database; however, both study teams have expressed interest in collaboration with the GA²LEN-birth cohorts on asthma and atopic diseases.

Almost all studies that are included are investigating primarily asthma, allergic rhinitis and eczema as main outcomes. Six cohorts also examined food allergies: Isle of Wight, GINI-B, LISA, DARC and GEPSII 1 and 2. The investigation of environmental factors was emphasized by nine studies: the four AMIC Studies, ECA, BAMSE, MAAS, GINI-B and LISA, some studies

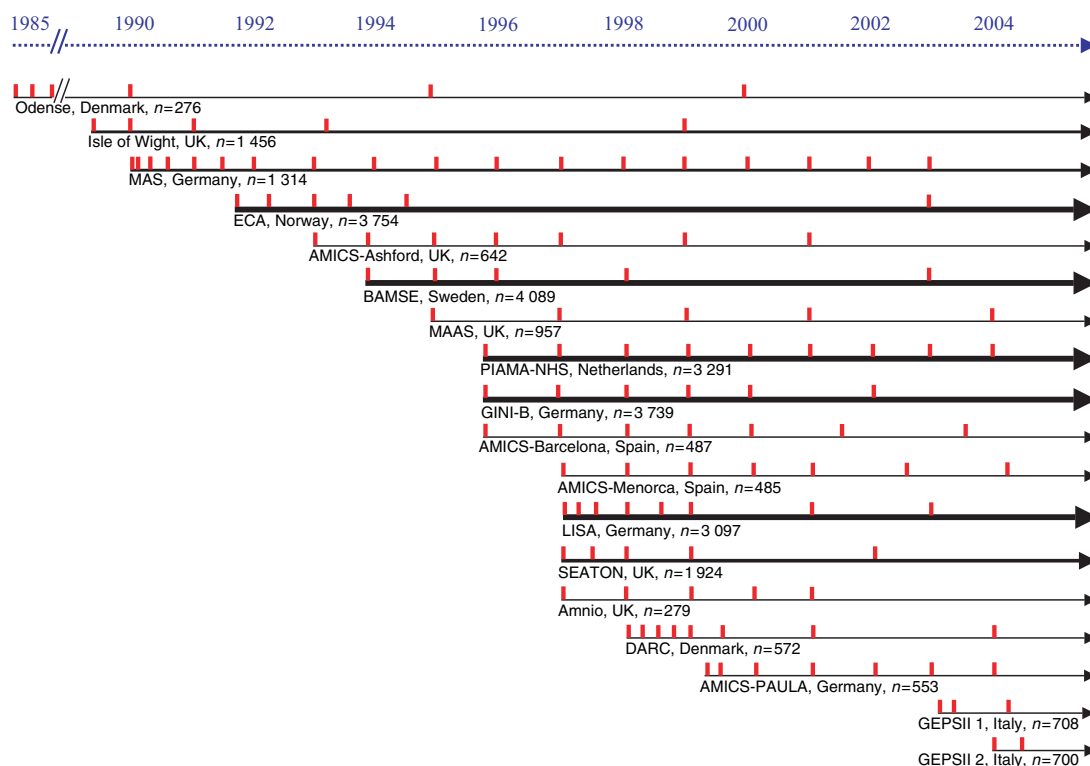


Figure 2. European birth cohorts designed to examine asthma and atopic diseases: short study name, country, baseline number of participants and time points of follow-up (vertical bars).

collected very detailed information on housing, not only by questionnaires but also by extensive home visits (ECA, BAMSE, MAAS, LISA). SEATON has been particularly examining the influence of diet on allergic disease (Table 1).

In general, the study settings were in urban, particularly metropolitan areas. Only four birth cohorts included children from rural or mixed urban/rural backgrounds: the Dutch PIAMA-NHS, the German GINI-B and the two island-based studies (Isle of Wight and AMICS-Menorca). The majority of the birth cohorts recruited their children in university/academic teaching hospitals. Few chose health care centres (BAMSE), family/prenatal care medical practices (AMICS-Ashford and -Menorca) or mid-wife practices (PIAMA-NHS) (Table 1).

Most studies have recruited unselected population-based birth cohorts. According to parental atopy or allergy status, some studies have purposely enriched their cohorts with 'high-risk' (MAS) or 'low-risk' children (PIAMA-NHS, recruitment independent of the PIAMA intervention study) (Table 1).

The follow-up rates at age 4 varied from 43% to 97% (14 cohorts) and at age 9–10 from 58% to 94% (five cohorts) in relation to all children recruited at baseline. They were considerably larger in the Scandinavian, Isle of Wight, MAAS, AMICS-Menorca and -PAULA cohorts (all single-centre studies) and the Dutch multi-centre

PIAMA-NHS compared with the three German multi-centre cohorts (MAS, GINI-B, LISA). The lowest follow-up rates were recorded in the AMICS-Barcelona (43%) and the Amnio-Study (54%), both at age 4 (Table 2).

Principal investigators of the European birth cohorts on asthma and atopic diseases are either clinical researchers (paediatricians, allergists) or work for regional/national institutions as epidemiologists, environmental or public health researchers. The primary funding of all European birth cohorts on asthma and atopic disease came from public sources. Most studies manage and analyse their data using Microsoft ACCESS, SPSS or SAS, others use Splus or STATA. None of these software packages presents a barrier for a potential exchange of individual data (Table 2).

Discussion

The present review (part I) compared study designs of 18 European birth cohorts designed to examine asthma and atopic disease. The previous experience of the Asthma UK Early Life Task Force assessing birth cohorts on asthma in the UK was a useful prerequisite for establishing a common database of European birth cohorts. The great interest of the participating European research teams to collaborate encouraged us to establish a

Table 1. European birth cohorts designed to examine asthma and atopic diseases: study names (with reference to publication of study design), main objectives (A, asthma; AR, allergic rhinitis; E, eczema), study settings, recruitment location and selection of participants

Study name	Main objectives	Start	Setting	Recruitment location	Selection of participants
Odense 1985 (8)	A, AR, E, sensitization (natural course; risk factors)	1985	Odense (Denmark)	University hospital	Unselected (population-based)
Isle of Wight (9)	A, E, food allergies (environmental factors)	1989	Isle of Wight (UK)	Antenatal clinic in one hospital	Unselected (population-based)
MAS (10) – Multicenter Allergy Study	A, AR, E (natural course; risk factors)	1990	Berlin, Duesseldorf, Freiburg, Mainz, Munich (Germany)	6 university hospitals	Enriched with 'high-risk' children (population-based)
ECA (11) – Environment and Childhood Asthma	A, AR, E (environmental factors)	1992	Oslo (Norway)	2 main hospitals (90% of all deliveries)	Unselected (population-based)
AMICS-Ashford (12) – Asthma Multicentre Infant Cohort Study	A, AR, E (environmental factors)	1993	Ashford, Kent (UK)	3 family medical practices	Unselected (population-based)
BAMSE (13) – Children, Allergy, Milieu, Stockholm, Epidemiolog. Survey	A, AR, E (environmental factors)	1994	Stockholm (Sweden)	58 healthcare centres in four districts	Unselected (population-based)
MAAS (14) – Manchester Asthma and Allergy Study	A, AR, E (environmental factors)	1995	Manchester (UK)	Antenatal clinics in two hospitals	Unselected, except for 'high-risk' children* (population-based)
PIAMA-NHS (15) – The Prevention and Incidence of Asthma and Mite Allergy - Natural Hist. Study	A, resp. allergy (incidence; risk factors)	1996	Northern, Central and Western Netherlands (NL)	52 mid-wife practices (incl. 12 from Rotterdam)	Enriched with 'low-risk' children (population-based)
GINI-B (16) – German Infant Nutritional Intervention-Study (observational part)	A, AR, E, food allergies (natural course; environmental/other risk factors)	1996	Munich and Wesel (Germany)	Munich: 8 hosp. (2 university) Wesel: 7 hospitals	Unselected, except for 'high-risk' children* (population-based)
AMICS-Barcelona (17) – Asthma Multicentre Infant Cohort Study	A, AR, E (environmental factors)	1996	Barcelona (Spain)	District hospital	Pregnant mothers during last trimester attending obstetric department (hospital-based)
AMICS-Menorca (17) – Asthma Multicentre Infant Cohort Study	A, AR, E (environmental factors)	1997	Island of Menorca (Spain)	All prenatal care general practices	Unselected (population-based)
LISA (18) – Lifestyle-related Factors on the Immune Syst./Development of Allerg. in Childhood	A, AR, E, food allergies, sensitization (natural course; risk factors; East vs West Germany)	1997	Leipzig (East-Germany), Munich, Wesel and Bad Honnef (West-Germany),	Leipzig: all 4 obstetric dept. Munich: 6 hosp. Wesel: 3 hosp.	Unselected (population-based)
SEATON (19) – Study of Eczema/ Asthma to observe Influence of Nutrition	A, AR, E (diet)	1997	Aberdeen (UK)	Antenatal clinic in 1 hospital	Unselected (population-based)
Amnio-Study – Amniocentesis Study	A, AR, E (cytokines/allergens in amniotic fluid)	1997	Southampton (UK)	Antenatal clinic in 1 hospital	Only pregnant mothers with amniocentesis
DARC-Study – Danish Allergy Research Council	A, AR, E, food allergies (incidence, prevalence)	1998	Odense (Denmark)	University hospital	Unselected (population-based)
AMICS-PAULA Asthma Multicentre Infant Cohort Study	A, AR, E (risk factors, genotypes)	1999	Munich (Germany)	Academic teaching hospital	Unselected (population-based)
GEPSII 1 – Gene and Environment: Prospective Study on Infants in Italy 1	A, AR, E, food allergies, obesity, neurodevelopmental disorders (risk factors, genotypes)	2003	Rome (Italy)	2 large hospitals	Unselected (population-based)
GEPSII 2 – Gene and Environment: Prospective Study on Infants in Italy 2	A, AR, E, food allergies, obesity, neurodevelopmental disorders (risk factors, genotypes)	2004	Bologna (Italy)	1 large hospital	Unselected (population-based)

*High-risk' children were recruited only if families did not participate in an intervention study/study arm.

Table 2. European birth cohorts designed to examine asthma and atopic diseases: number of participants at baseline, follow-up rate (in % of initial participants), type of coordinating institution, main source of funding and format of data management/analysis

Study name (<i>n</i> , country)	Follow-up rate, % (age in years)	Coordinating institution	Primary source of funding	Data management/ analysis (format)
Odense 1985 (276; Denmark)	79 (15)	University hospital (allergy centre)	National research fund	SPSS
Isle of Wight (1456; UK)	94 (9–10)	District general hospital	National research foundation	SPSS
MAS (1314; Germany)	58 (13)	University hospital (paediatric dept.)	National ministry	SPSS
ECA (3754; Norway)	84* (10)	University hospital (paediatric dept.)	National research council/university	SPSS
AMICS-Ashford (642; UK)	92 (8)	University hospital (environm./occup. medicine dept.)	Occupational health research foundation	SAS Splus STATA
BAMSE (4089; Sweden)	84 (9)	University hospital (environmental health dept.)	Regional and research councils	ACCESS STATA
MAAS (957; UK)	94 (5)	Academic teaching hospital	National research foundation	ACCESS SPSS
PIAMA-NHS (3291; the Netherlands)	88 (6)	National public health institute	National ministry	SAS
GINI-B (3739; Germany)	64 (4)	National research centre for environmental health	National ministry	SAS
AMICS-Barcelona (487; Spain)	43 (4)	Municipal research institute	National research council	Spluss
AMICS-Menorca (485; Spain)	96 (4)	Regional health authority	National research council	Spluss
LISA (3097; Germany)	80 (4)	National research centre for environmental health	National and regional ministries	SAS
SEATON (1924; UK)	65 (4–5)	University hospital (environm./occup. medicine dept.)	National research foundation	ACCESS SPSS
Amnio-Study (279; UK)	54 (4)	University hospital (paediatric dept.)	National research foundation	SPSS
DARC-Study (572; Denmark)	93 (3)	University hospital (allergy centre)	National research council	SAS SPSS
AMICS-PAULA (553; Germany)	97 (2)	University hospital (paediatric dept.)	Regional ministry	ACCESS SAS
GEPSII 1 (708; Italy)	1st follow-up is ongoing	Health authority (epidemiology dept.)	National ministry	ACCESS STATA
GEPSII 2 (700; Italy)	Recruitment is ongoing	Health authority (epidemiology dept.)	National ministry	ACCESS STATA

*In relation to $n = 1215$ with follow-up >2 years (original cohort $n = 3754$).

common database. We were able to assess 18 birth cohorts with information on all relevant characteristics regarding study design, objectives, potential predictors and outcomes for asthma and atopic disease, including the number of participants for every parameter at each follow-up.

Study aims and recruitment of participants

The European birth cohort studies aimed at examining the incidence, prevalence, natural course and risk factors for asthma and atopic diseases. As most study teams chose metropolitan areas or major cities for their setting, they will only be able to calculate estimates for these urban or metropolitan areas. Asthma and respiratory allergies seem more common in urban than in rural areas (20–22). The incidence and prevalence estimated from studies with urban settings may, therefore, overestimate the number of affected children in the general population of a country.

Several studies recruited children from university or academic teaching hospitals. This could be representative of a particular city or region, if the obstetric department is the only one in the area. For example, the Danish studies ('Odense 1985' and DARC) recruited their newborns from the Odense University Hospital where most children of that region are born, and the

Norwegian ECA study recruited children from the two major hospitals in Oslo, covering 90% of all deliveries. However, in many large European cities different types of hospitals exist, where university hospitals are more likely to admit a higher proportion of mothers with high-risk pregnancies/deliveries than other hospitals. Children recruited in academic teaching hospitals would differ from children born in nonacademic hospitals and may not be representative of the general population. This could be of concern for some studies such as the MAS, which included only children from German university hospitals.

Findings of a birth cohort study need to be interpreted carefully if the selection of participants is linked to the recruitment process for an intervention study. Intervention studies examining the efficacy of allergy preventive measures require children 'at risk' for allergies (e.g. from parents with asthma/atopy). Families who are willing to participate in preventive intervention studies on allergic diseases could differ from less interested families, e.g. higher socioeconomic status, higher risk of allergies and better motivation to follow a strict intervention study protocol (23). 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 nonresponse bias, it is important to

determine whether the recruited study population differs from the source population. Several birth cohort studies did not have information on the assembly of their samples, such as the number of: (i) all babies born in the study centres during the recruitment period, (ii) eligible children fulfilling the inclusion/exclusion criteria, and (iii) parents nonresponding or actively refusing to participate.

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, migration, losing interest or refusing to participate, particularly in cases of invasive diagnostic tests. The follow-up rates in relation to all participants at baseline refer to the highest proportion of available data at the corresponding time point (usually from questionnaires, available data from blood or lung function tests could be lower). Some investigators indicated that allergic or 'high-risk' children were less likely to drop out of their studies than healthy children, because parents of allergic children or who are allergic themselves were more aware of the potential benefit. Other investigators assumed that especially families with allergic children seemed to drop out more because the study participation was perceived as an additional burden to already many doctor/hospital visits. However, low follow-up rates can affect the potential generalizability of the results by possible selection bias (if remaining children differ from those lost to follow-up). Furthermore, lower numbers of study participants will reduce the statistical power of the analyses. Particularly, the Scandinavian studies (ECA, BAMSE, DARC, 'Odense 1985') and the German AMICS-PAULA study were able to maintain high follow-up rates. Apart from having a study team that is highly successful in keeping contact with families and tracking down those who moved away, it could be due to the fact that they are single-centre studies. On the other hand, the Dutch PIAMA-NHS as a multi-centre study was also able to maintain high follow-up rates. The logistic possibilities of a large national public health institution could be one explanation, in addition to the quality of the study team. The German MAS managed to slightly increase the number of participants compared with previous assessments by offering a 15 Euro voucher for 12- to 13-year-old children to come in for interview and physical examination.

To our knowledge, there is no systematic review on methods to increase response rates in cohort studies with children or their parents. However, a recent meta-analysis of 292 intervention trials (250 000 participants combined) has examined methods to increase response rates to postal questionnaires. The most effective strategies (all statistically significant) were: questionnaires sent by recorded delivery *vs* normal mail [odds ratio (OR) 2.2],

monetary *vs* nonmonetary incentives (OR 2.0), short *vs* long questionnaires (OR 1.9), incentives not related to responding (OR 1.7), contacting participants before sending questionnaires (OR 1.5), use of coloured ink (OR 1.4), providing nonrespondents with a second copy of the questionnaire (OR 1.4), stamped return envelope (OR 1.3) (24).

Strengths and limitations

Although we were able to identify 18 European birth cohort studies on asthma and atopic disease, we may have missed others, possibly studies which presently have not published any data or are still in the planning process. Work on the GA²LEN-work package 'birth cohorts' is in progress, and further European research teams conducting or planning birth cohorts on asthma and atopic disease are encouraged to join this initiative. Information on new birth cohorts or further data of existing studies can easily be entered in the database.

A strength of the present project was the detailed assessment of study characteristics by personal visits/communication. By interviewing all present study team members and joined reviewing of questionnaires and databases it was possible to obtain a level of detailed information far exceeding that possible through extracting information from publications or postal questionnaires. The collaboration has been excellent between all participating European birth cohorts on asthma and atopic diseases and a trustful basis has been created for future common research activities. Pooling data for meta-analyses would increase the statistical power and might allow the examination of less common exposures for allergic diseases. A possible limiting factor could be the nonstandardized assessment of exposure and outcome variables between studies. In a subsequent review (part II) we will compare the assessment of objective/subjective outcome and relevant exposure parameters, and discuss the possibility of pooling data for meta-analyses.

Conclusions

- An excellent collaboration has emerged between the participating research teams of the GA²LEN-Work Package 'Birth Cohorts'.
- It was possible to establish a common database assessing relevant characteristics of 18 European birth cohort studies on asthma and atopic diseases.
- Most birth cohorts have been initiated in urban/metropolitan settings.
- Many studies maintained high follow-up rates, even after five or more years.
- Public sponsorship is essential for the continuation of existing and the initiation of future birth cohort studies examining asthma and allergic diseases.

- The common database of European birth cohorts in the GA²LEN project is a useful basis for evaluating the possibility to pool data and performing meta-analyses. Furthermore, it can facilitate the planning and realization of future birth cohorts on asthma and atopic diseases.

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