Current research and funding in the EU25 countries in the area of asthma in children

Fast-track study initiated by the Joint Research Centre of the European Commission

Authors: Rosemarie Felder-Puig MSc, Clauda Wild PhD – Academy of Sciences, Vienna, Austria

Background

There has been a dramatic increase in paediatric asthma rates over the last few decades. Despite the development of effective treatment options and innovations in patient education and trigger avoidance, the chronicity of the disease in a considerable proportion of patients poses an important socio-economic problem. There is increasing evidence that an interplay of genetic predisposition and environmental exposure to a number of agents, including air pollutants, allergens and infectious agents, are operative in the inception and persistence of the clinical asthma phenotype. Therefore, future research has to be performed with large cohorts that are appropriately genotyped, and their environment will then need to be monitored in relation to all possible environmental risk factors. Given the current limited research funding possibilities in a number of European countries, it may be necessary to direct and organise such research activities on a European level.

Objectives

This fast-track study is aimed at the identification of the amount of on-going research on asthma-related topics and the allocation of funding for such research. It focuses on EU25 countries and is restricted, as much as possible, to research on genetics and environmental factors in paediatric asthma.

Search strategy

Our search strategy was based on three approaches: (1) To review the most recent scientific work published by EU25 investigators and identify those publications that address genetic and/or environmental factors in paediatric asthma; (2) To look for databases on the topic that are accessible via Internet; (3) To identify those researchers that have been active in this field of research and to contact them by e-mail about ongoing projects and the funding of these projects.

Overview of research acitivity within EU25 – recently published work

Our fast-track study presents a summary of scientific articles published by scientists of EU25 countries. We performed a PubMed search, using the keywords „asthma“ and

„children“. Considering the huge number of publications, we limited our search to papers published during the past 14 months, starting in January 2002. A total of about 1,200 articles worldwide could be identified for this period of time, of which 389 were published by researchers of EU25 countries (see Table 1 in the appendix). Of these 389 papers on paediatric asthma, 104 addressed genetic and/or environmental factors. About three quarters were original reports and are presented in the references, the rest were review articles. We give a short summary of the contents of these original reports including the affiliations of the first authors.

Recent publications of EU25 researchers about genetic factors in childhood asthma

Researchers of the *University of Antwerp* identified a new subtype of circulating dentritic cells in peripheral blood of children and found a decreased rate of these cells in asthmatic children [29]. Czech researchers of the *University of Brno* investigated whether specific variants of the gene for IKAP were associated with bronchial asthma in children but found no evidence for that in a homogenous Czech population [60].

MAS90 research teams of the *Charité Berlin* published about different gene polymorphisms and their association with childhood asthma [61,62]. Researchers of the *Ludwig Maximilians University Munich* evaluated the associations between specific polymorphisms and allergy in large populations of German school children and identified novel polymorphisms in IL4 gene [41,42]. In another study, they found that the heterozygosity of the alpha1 antitrypsin genotypes MS or MZ, or low alpha1-AT plasma levels, were not associated with an increased risk of developing asthma [23]. Another German research group active in exploring genetic factors, were from the *University of Freiburg*: They investigated whether uteroglobin-related protein 1 (UGRP1) was associated with the development of asthma in a sample of German children but found no association [31] nor did they find an association beween asthma and a promoter polymorphism in the CD14 gene [33]. In another study, they compared the same gene variant in TH1 and TH2 chronic inflammatory diseases [32|.

Researchers of the *Semmelweis Medical University at Budapest* revealed an important role of mannose-binding lectin alleles in the susceptibility to asthma in children infected with C pneumoniae in one study, and of the tumor necrosis factor system on the pathomechanism of bronchial hyperreactivity in another study [52,30]. Italian scientists of the *University of Verone* found no association between the interleukin-4 receptor alpha gene and a predisposition to atopic asthma in children from north-east Italy [51].

Scientists of the *University of Aberdeen* sought to determine the influence of the CCR5Delta32 mutation, which has been shown to be associated with a reduced prevalence of asthma in childhood, on asthma and allergy in the transition from childhood to adulthood

[65]. They found that this „protective effect“ is obviously lost in the transition between childhood and early adulthood. Genetic researchers of the *University of Southhampton* intended to identify novel promoter polymorphisms within specific genes and to determine their role in asthma susceptibility, and found that polymorphisms in the IL-4 and IL-4 alpha chain genes but in no other analyzed polymorphisms contribute to conferring susceptibility to and modulating severity of asthma [58,59,7]. Their colleagues of the *University Hospital of North Staffordshire* hypothesized that GSTP1 genotypes in the mother and child, but not the father, mediate asthma phenotypes in the child [19]. They found that in mothers, but not fathers, Val105/Val105 genotype was associated with a reduced risk of airway hyperresponsiveness in the child. In another paper, they described a method for the correction of dose-response slopes and PC20 values baseline parameters in children, and illustrate the effect of such corrections on the association of airway hyperresponsiveness with the GSTP1 Ile105Val polymorphism in children [20]. A consortium of European researchers collaborated on a project about positional cloning of a novel gene influencing asthma from chromosome 2q14, and results were published by a scientist of the *British Oxagen* [1]. Genetic researchers of the *University of Oxford* published their findings about positional cloning of a quantitative trait locus on chromosome 13q14 that influences immunoglobulin E levels and asthma [74]. Researchers of the *University of Belfast* found that the proinflammatory activities of Interferon gamma may play an important role in the pathogenesis of childhood asthma, suggesting that asthma is not simply a Th2 driven response [14].

Recent publications of EU25 researchers about environmental factors in childhood asthma

A study originating from the *Catholic University of Louvain at Brussels* focused on the hypothesis that the increasing exposure of children to chlorination products in indoor pools may be an important cause for the rising incidence of childhood asthma [8]. Investigators of the *Danish Epidemiology Science Centre at Copenhagen* evaluated the effect of childhood vaccinations on the development of allergy and asthma [5,6]. They found that smallpox vaccination was associated with a slightly decreased risk of asthma and that age at BCG vaccination in childhood did not influence the development of asthma.

French investigators of the *CHU Grenoble* examined the relationships betwen several markers of allergy and asthma severity in 215 asthmatic children below age 16 and found a positive relationship between asthma severity and high levels of total IgE but not with blood eosinophil counts [64]. Results of the Vesta study, published by a scientist of the *CHU Nancy*, indicated that exposure to traffic exhausts of young children can be associated with the development of asthma [75].

A study of the *Finnish National Public Health Institute at Kuopio* evaluated the association between serum mold-specific IgG levels in primary school children with asthma, wheezing, or cough symptoms and exposure to indoor mold in 2 schools with and without mold damage, and found that IgG analysis cannot be readily suggested as a routine method for the evaluation of these exposures [36]. Scientists of the same institution tested the hypothesis that maternal sex hormone concentrations during early pregnancy are associated with the risk of onset of asthma in the child but did not find a significant relationship [72]. Their colleagues at the *Finnish University of Oulu* evaluated the controversal role of early respiratory syncytial virus infection in allergic sensitization and found that an early RSV infection results in a reduction of skin prick test positivity but not in a reduced occurence of atopic disease [40].

Researchers of the *Centre for Public Health at Berlin* assessed the combined effects of chronic exposure to traffic-related air pollution and noise upon the risk of skin and respiratory diseases in children [37]. Their results suggest a significant risk for asthma with increasing traffic load. Scientists of the *German GSF* found no convincing association between maternal oral contraceptive use and atopic diseases in children [26]. The *German MAS90 group* analyzed prevalences of allergic sensitization and atopic disease in relation to vaccination coverage and found that children with a higher vaccination coverage seemed to be transiently better protected against development of atopy in the first year [27].

The research team of Erika von Mutius at the *Ludwig Maximilians University Munich* evaluated the relationship between traffic exposure and inception of atopy in large random samples of school children [54]. They found that high vehicle traffic was associated with asthma, cough and wheeze, and in children additionally exposed to environmental tobacco smoke, with allergic sensitisation. In another study, they addressed the interdependencies of exposue to furred pets in infancy and the prevalence of asthma, and found that allowing cats to be in the child's bedrom from the first year of life onwards may be an indicator of intensive exposure to cats and appears to prevent the development of childhood asthma [56].

Researchers of the *UFZ - Centre for Environmental Research at Leipzig* presented two publications: One was about the influence of redecoration of the appartment on airway symptoms in infants during the first two years of life, and it suggested a significant assocation between redecoration of the apartment and obstructive bronchitis in the infant [22]. Another study assessed the influence of spatial and temporal variations in the urban air pollution profile on asthmatic disease in young children [25]. Depending on the level of traffic (high or low), children residing in areas with a dominant coal-heating emission profile had more frequently a diagnosis of asthma. The *Insitute for Environmental Research at Duesseldorf* performed a study about the impact of environmental tobacco smoke on atopic eczema, allergic sensitization and allergic airway diseases in a large sample of school beginners [45].

Regarding asthmatic children, they found no significant association between a history of asthma and tobacco smoke exposure.

Investigators of the *Agency for Public Health at Rome* searched for an association between socioeconomic factors and childhood asthma in a large sample included in the ISAAC study [17]. They found that socioeconomic conditions are associated with asthma severity and hospitalisation, and to a lesser extent with asthma occurence. Another study performed by the same organization investigated respiratory symptoms and dietary factors in a large sample of 6-7 year old children and revealed that dietary antioxidants in vegetables may reduce wheezing smptoms, whereas butter and margarine may increase these symptoms [24]. Their colleagues at the *Italian „Instituto Auxologico" at Verbania* compared two samples of adolescents living in areas with and without air pollution, and found that exposure to air pollutants may have an impact on the prevalence of bronchial aspecific hyperresponsiveness in otherwise normal children [47]. Paediatricians of the *San Camillo de Lellis Hospital at Rome* investigated the association between infective and uterus related complications during pregnancy and included children with asthma and controls in their study [16]. They found that prenatal infective complications (influenza and fever episodes in the mother) may contribute to the development of asthma in the child, and suggested exposure to isoxsuprine as a possible new risk factor for asthma.

Researchers of the *Kaunas University in Lithuania* tried to assess the relationship between respiratory and allergic symptoms in 6-7 year old children and air pollutants but found no differences amongst children living in four different districts of Kaunas [67].

Scientists of the *Erasmus University at Rotterdam* assessed the impact of birth order and sibship size but found no significant relationship with asthma [9]. Their colleagues of the *Dutch National Insitute of Public Health and the Environment* found that in pre-school children frequent consumption of products containing milk fat is associated with a reduced risk of asthma symptoms [71]. The same institution presented a paper about the impact of mite-impermeable mattress encasings on dust and mite allergene levels of mattresses and found a significant but modest effect [66].

Investigators of the *Polish Medical University of Silesia* sought to explore predictors of childhood asthma in a 7-year-longitudinal study of 663 children and found that only parental asthma and using coal for cooking were significant predictors whereas the effect of exposure to parental smoking was not significant [73]. A research group of the *Polish University of Wroclawiu* found a significantly higher prevalence of bronchial asthma in a mould-sensitive group of patients as compared to the mould-insensitive subjects [10].

Portuguese paediatricians of the *Francisco Xavier Hospital at Lisbon* revealed that asthmatic children were less likely to be carriers of Haemophilus influenzae and Streptococcus pneumoniae [53]. Investigators of the *Institute of Medical Research Barcelona*

found that SO_2 levels in 6 different big European cities are associated with asthma hospital admissions in children, suggesting that a reduction in air pollution could lead to a decrease in the number of asthma admissions in children [68]. Their colleagues of the *University Carlos III at Madrid* assessed the short term effects of different types of allergenic pollen on asthma emergiences in the area of Madrid during a period of 3 years, and found an association between pollen levels and asthma-related emergencies, irrespective of the effect of air pollutants [69].

Scientists of the *Karolinska Institute at Stockholm* tried to elucidate how early exposure to cat and dog relates to IgE-sensitization and asthma in children at 2 and 4 years of age [2]. They found a lowered risk for asthma at the age of 4 when being early exposed to dog but not to cat. These controversial findings were questioned by the same group in another study addressing a selection bias of pet exposure [3]. It turned out that cats were less frequently kept in families with parental asthma, and that families with smoking mothers and those with low socioeconomic index kept cats and dogs more frequently. Another study addressed 3 factors of family lifestyle (breastfeeding, maternal tobacco smoke, home dampness) in agreement with allergy preventing guidelines on wheezing and asthma in 2-year-old children [70]. Among children with no heredity, family lifestyle according to the guidelines gave a twofold reduction of asthma, while the group with heredity had a threefold reduction. A fourth study of this group challenged the hypothesis that Epstein-Barr virus may play a role in the pathogenesis of allergic diseases, which could not be confirmed [63].

Paediatricians of the *Huddinge University Hospital at Stockholm* found an overall trend towards a slightly increased prevalence of bronchial asthma in young children of mothers who were highly exposed to birch pollen during pregnancy as compared to those with low exposure [43|. Their colleagues of the *Swedish Lingkoping University* found no association between 3 different types of pertussis vaccination in infancy and allergic manifestation at the age of 7 [55]. At the same institution, a study about allergen-induced cytokine secretion was performed [12]. Results suggested that children with atopic asthma produced higher levels of allergen-induced IL-4 and IL-9 than controls, and that high levels of eosinophilia-associated IL-5 responses are induced by cat and dog allergen in both atopic and non-atopic asthmatic children. Two other studies of Lingkoping University scientists found an association between high BMI and asthma severity in children [48] and a double risk for the development of asthma in children born at very low birth weight as compared to term children [49].

Researchers of *Goteborg University* found that cat-keeping was associated with a modified Th2 response, producing IgG4 but not IgE antibodies [34]. This immune response was not associated with an increased risk of asthma or allergy. Their colleagues of the *Swedish Orebro University* followed 904 children from the age of 3 months to 4 years [Gustafsson]. Features of housing and early feeding patterns were found to have limited

effect on the development of allergies in the children. Early exposure to furry animals seemed to prevent the development of asthma. Researchers of the *Mid Sweden Research and Development Centre* found a lower risk of allergic rhinitis in persons of 3 different cohorts whose parents were infolved in farming whereas the protective effect of growing up on a farm on the risk of asthma was visible only in a later cohort [13]. Researchers of the *Swedish DBH Study Group* investigated the association between pet-keeping at the time of birth and allergic symptoms in young Swedish children and found that the distribution of pet-keeping in the population was largely explained by avoidance behaviour, meaning that mostly families without a history of allergy actually were keeping a pet [11].

Researchers of the *University of Leicester* published data about the population attributable risk, a measure of the excess risk of disease associated with a risk factor for some of the common adverse health effects, for example childhood asthma, that have been associated with exposure of children to environmental tobacco smoke [57]. Researchers of the *David Hide Asthma and Allergy Research Centre* presented two publications: One study showed that strict allergen avoidance in infancy in high risk children reduces the development of allergic sensitisation to house dust mite, which may prevent some cases of childhood asthma [4]. Another study investigated the role of environmental and hereditary factors in determining whether persistent childhood wheezing phenotypes had an early or late onset [46]. The authors found a predominant impact of inheritance on persistant childhood wheeze.

Authors of the *University of East Anglia at Norwich* performed a cross-sectional postal survey of 6,500 households to evaluate the health effects of air pollution [35]. They revealed a complex relationship between actual levels of pollution, social deprivation, socio-behavioural factors and people's perceptions about pollution. Colleagues from the same university undertook a study to determine the relationship between genetic factors, early life environment exposures, and the prevalence of atopic disorders in infants [39]. Infant asthma was significantly associated with the report of a serious chest infection before age 3, an asthmatic mother, and an asthmatic sibling.

Researchers of the *University of Newcastle upon Tyne* explored the health and environmental concerns of parents living close to opencoast coal mines in the UK and characterised parental risk perceptions in relation to children's asthma status [50]. Colleagues of the *University of Wales at Cardiff* used the data of the ISAAC study to investigate the relationship between pollen exposure and allergic symptoms among children in different countries and found a weak but consistent tendency for the prevalence of allergic symptoms to be inversely associated with pollen exposure [15].

Researchers of the *University of Birmingham* examined the relationships among maternal smoking in pregnancy, fetal development, and the risk of asthma in childhood, and

found that maternal smoking in pregnancy increases the risk of asthma during the first 7 years of life, and that only a small fraction of the effect seemed to be mediated through fetal growth [38].

Scientists of the *Imperial College of London* questioned the assumption that frequent antibiotic prescriptions in early life are associated with the development of asthma [21]. They found significant relationships between antibiotic use in childhood and asthma in adulthood, but these were largely confined to antibiotics prescribed for lower respiratory symptoms, that may also suggest a tendency for prescriptions for the early manifestations of preexisting asthma. Researchers of the *University of Southhampton* found that high exposure to the air pollutant nitrogen dioxide in the week before the start of a respiratory viral infection, and at levels within current air quality standards, is associated with an increase in the severity of a resulting asthma exacerbation [18].

Databases accessible via Internet

Information about ongoing research projects and their funding is not easily available. Some organisations (e.g., UK's National Asthma Campaign, the European Union, the German GSF, or the University of Leicester) present brilliant documentation of ongoing projects including funding on their websites, while others display only references of published work, if any. Therefore, our search for information had to rely heavily on personal communication with the scientists concerned.

Overview of research activity within EU25 – ongoing projects

We sent out e-mails to about 230 scientists in EU25 countries who were identified as being active in the field of paediatric asthma. They were asked to give us a short description of ongoing projects about genetic and/or environmental factors and to tell us from where they received the funding. The response rate was approximately 50%, which is quite good considering the usual working load of scientists and the fact that they had only about two weeks' time to answer. The highest response rates could be observed in scientists from Belgium, Denmark, Hungary, Poland, and Slovakia, and the lowest in scientists from Finland, France, and Italy. Two top researchers, one from Germany and one from Great Britain, told us that they do not want to display confidential information about their projects.

The following summary of ongoing work is based on the information we received from the scientists as well as the on the information displayed on the websites of some organizations. For some of the mentioned projects, data collection has been finished, but analyses still go on, that will result in new publications.

Projects on genetic factors

The *German GSF – Research Centre for Environment and Health* is one of Europe's most active institutions involved in research about genetic and environmental factors in childhood asthma. GSF projects are usually financed from national public sources or in the context of EU projects. No funds are received from pharmaceutical industry or private organizations. The GSF is involved in a couple of projects aimed to identify novel genes associated with allergy and asthma susceptibility, and to assess genetic determinants in the context of functional relevance and clinical importance. These projects are partly conducted with collaborators of the *German „National Genome Research Network"*. Funding is mainly provided by the German Ministry of Research, with additional contributions from other public institutions.

One project of the German National Genome Research Network about the genetic determinants of asthma and atopic diseases is coordinated by a genetic researcher of the *Ludwig Maximilians University at Munich*. It is called „Multicentre Asthma Genetics in Childhood (MAGICS)" and involves a couple of centres in Germany and Austria. One other important participating institution is the *Charité-Humboldt University at Berlin*. Their top researchers are also involved in the GA2LEN Network of Excellence and coordinate a birth cohort study that will be funded by the EU with up to EUR 100,000 a year.

Researchers of the *Hungarian University of Szeged* test for associations between atopic bronchial asthma and specific genotypes of various single-nucleotide polymorphisms using age-matched analysis and population-analysis. Estimated total costs of this project amount to more than 200,000 Euro, of which 10% are contributed by a scientific grant. Their colleagues from the *University of Debrecen* perform cellular and molecular biological experiments studying the regulation of inflammtory gene expression in airway epithelial cells. This 4-year-project received a contribution of EUR 37,000 from the Hungarian Scientific Research Fund, the salaries are borne by the university.

Projects on environmental factors

Microbes / Infections

Researchers of the *Ludwig Maximilians University Munich* perform a study about „Microbes and parasites in a farmer's environment as protectors against allergic disease in childhood" on behalf of the Bavarian Ministry of Health. They also coordinate the EU-project PASTURE (Protection against Allergy: Study in Rural Environments) that involves 8 institutions from Germany, Austria, Finland, Netherlands, and Switzerland, and is supported by the EU with EUR 2 million for 4 years.

Greek scientists of the *University of Athens* conduct a number of in-vitro studies about the effects of rhinovirus on different aspects of paediatric asthma. Funding was provided by

the university (45%), pharmaceutical industry (31%), the hospital (12%) and an international award (12%).

A British researcher of the *University of Nottingham* studies the relation between atopy, asthma and parasite infection in urban and rural populations of central Ethiopia. Findings of this research will be used to identify new ways of treating or preventing asthma in the developing and developed world. UK's National Asthma Campaign contributes EUR 65,000 to this research.

Allergens

Scientists of the *Environmental and Health Research Unit at Barcelona* have been participating in the Asthma Multicenter Cohort Study (AMICS). It evaluated early exposures to allergens and irritants and the risk of developing asthma and atopy and includes a birth cohort of 1,600 children, of whom also DNA was collected for further studies about genetic-environmental interactions. The project was funded by a Spanish public organization and FP5 of the EU.

Researchers of the *University of Utrecht* informed about the PIAMA study (prevention and incidence of asthma and mite allergy), which is about the prevention of asthma/allergy by mite-impermeable covers, and the identification of other environmental risk factors by following up a large cohort of unselected children from birth. This project whose total costs amount to EUR 2 million was financed by the Dutch Asthma Fond, the National Science Foundation, the Ministry of Environment, and the EU.

Investigators of the *Polish Medical University of Lodz* evaluate exposure and hypersensitivity to indoor allergens (cockroach, mouse, cat, dust mites, and molds) in asthmatic children and the influence of anti-allergen interventions in families' homes on the clinical manifestation of the disease. The total costs of about EUR 146,000 are borne by the Polish State Committee for Scientific Research.

Portuguese researchers of the *D'Estefania Hospital at Lisbon* perform a 10-year-prospective study about persistent versus transient cow's milk allergy as risk factor for asthma and other allergic diseases. Another research project of this group addresses the relationship betwen exposure to pets and atopic sensitization and asthma symptoms occurence. All these studies are self-funded and financed by the hospital.

Swedish researchers of the *Huddinge University Hospital Stockholm* study the influence of pet exposure on airway inflammation of children with a specific asthma phenotype. Costs are borne by the university (30%), private organizations (60%), and pharmaceutical industry (10%). Another study evaluates the exposure to birch pollen in association with the development of atopic disease in 1,000 children. This study has been funded by the university (30%), and private and public institutions (70%).

Slowak researchers of the *Institute of Preventive and Clinical Medicine Bratislava* assess allergy development in 8 environmentally different Slovak regions with respect to prenatal and postnatal environmental exposure to selected xenobiotics. Placental contamination is used as a proxy measure for in-utero exposure. The children are followed from birth to preschool age. The total costs of about EUR 200,000 are borne by the Slowak Agency for Science and Technology Promotion. These researchers have also taken part in a EU-funded project, coordinated by the *University of Bristol*, and entitled „Placental Uptake and Transfer of Environmental Chemicals Relating to Allergy in Childhood Years (PLUTOCRACY)". Other participating institutions are from Belgium, Romania, Slovakia, and the USA. The EU puts at disposal an amount of EUR 1.5 million for 3 years.

Allergy researchers at the *University of Southhampton* study the role of the placenta in predisposing children towards allergies. They test blood samples from pregnant women with and without asthma and look for the same substances in the placenta and the babies' blood after delivery. This study is funded by UK's National Asthma Campaign.

A scientist of the *North West Lung Centre at Manchester* is responsible for a study following the development of asthma and other allergic diseases in children who are at risk because both parents have allergies. This 3 years' study received a contribution of EUR 150,000 from UK's National Asthma Campaign.

A project coordinated by the *Imperial College of London* is called „Environmental influences and infection as aetiological agencies in atopy and asthma in young children". It examines the prevalence of allergens in the home environments including cat fur, house dust mite allergens and pollen, determines the levels of exposure to NO2 and tobacco smoke, and estimates the impact of diet in the early years of life. It is a multi-centre epidemiologic study involving seven centres across Europe, five birth-cohorts, and two cross-sectional populations of 6,500 children. The total costs for 10 years amount to EUR 3 million and are funded by the EU (15%), medical charities (50%), and government (35%).

Pollution

A study of the *German GSF* called INGA is about the impact of indoor factors (allergens, pollutants), and prevalence of asthma and allergic diseases in both adults and children, which has been financed by the German Ministry of Research.The *German UFZ* (Centre for Environmental Research Leipzig-Halle) has been performing various studies addressing the effects of indoor and outdoor air pollution, lifestyle, and exposure to moulds on asthma and allergic diseases in different age groups of children. Acronyms for their projects are: KIGA, LISS, LARS, LISA, ENV 14, AND LEIPI. Funding has been fully obtained from national public sources.

A researcher of the *Berlin Centre for Public Health* and collaborators initiated a study assessing whether long-term exposure of children to the combination of traffic noise and air

pollution results in more adverse health effects (physician contacts because of asthma and bronchitis) than exposure to air pollution alone. Funding for this study came from public sources with a minor contribution from a private organization.

Researchers of the *University Carlos III of Madrid* have evaluated the short-term effects of air pollutants and airborne pollen concentrations on asthma-related emergencies using an epidemiological time-series design. This study was financed by Madrid's Regional Health Authority.

Researchers of the *CHU Bordeaux* are involved in a project performed at six French cities to study the relationship between allergic diseases and indoor and outdoor pollutants in classrooms and schools. 50% of total costs are financed by the French Mininstry of Health, 40% come from private sources, and 10% are contributed by pharmaceutical industry. They also conduct a follow-up study of the ECRHS (European Community Respiratory Health Study) to show how environmental factors in childhood may influence adult respiratory health. This project received contributions from private organizations (60%) and pharmaceutical industry (40%).

Researchers of the *Polish University of Silesia* evaluate the association between vehicle-related pollution and asthma. They have been collecting data of about 13,000 children from a Polish town. The first part of the study with estimated costs of EUR 25,000 has been financed by municipality, the funding for the second part is still unresolved.

The traffic hypothesis has been questionned by researchers of *St George's Hospital Medical School* who conducted a study entitled „Trends in childhood asthma, eczema and hay fever in South East England", which was sponsored by UK's National Asthma Campaign with an amount of EUR 48,000.

Researchers of the *University of Leicester* assess the impact of particle pollution on the prevalence and incidence of respiratory disease in a cohort of 4,500 young children. The project did not receive external funding.

Scientists of the *Queen's University of Belfast* try to investigate whether glass fronted fires are assoicated with higher levels of pollutants and whether these pollutants lead to a worsening of respiratory symptoms. The study includes a sample of 100 adults and children with asthma living in houses heated by glass fronted fires and compared with a similar group in homes heated by other methods. The total costs of about EUR 500,000 are borne by the Northern Ireland Public Health Care.

Researchers of the *University of East Anglia at Norwich* informed that they continue their analyses on data collected about people's perception of the severity of air pollution, and the prevalence of respiratory symptoms including childhood asthma. The project has been financed exclusively from public sources (local government, local health authority, university).

Other life-style related factors

Investigators of the *University of Louvain at Brussels* have just completed a second survey on school children confirming the link between asthma or lung inflammation risk with both the cumulated and the very early exposure of children to trichloramine and other toxic chlorination by-products. The total costs of this research project, including studies in animals and humans on the acute toxicity of trichloramine, were approximately EUR 500,000. Funding could be obtained from public organizations including the EU-project HELIOS and a research project of the Brussels Capital Region.

The *German GSF* conducts a study called LISA about the influence of life-style factors on the development of the immune system and allergies in East and West Germany. It includes a prospective birth cohort in 4 regions of Germany that have been followed up since birth. Collaborators are 5 academic institutions from Germany. The study was funded by the Bavarian government and other public sources.

Researchers of the *Erasmus MC University Rotterdam* perform a study about the relationship between diphteria-tetanus-pertussis-poliomyelitis vaccination and ashma, allergy and eczema in primary school children. The estimated total costs of about EUR 100,000 are financed by university. The effect of BCG vaccination at birth on the risk of asthma and aotpy in children is studied by researchers of the *Wytenshawe Hospital at Manchester* who received financial support of about EUR 160,000 from UK's National Asthma Campaign.

A team of scientists at the *University of Aberdeen* investigates the links between diet and asthma. They look at the progress of 2,000 children whose mothers' diets were monitored during pregancy. Total costs amount to about EUR 550,000 of which 80% are funded by UK's National Asthma Campaign, and the rest by public Scottish organizations. Scientists of the *Imperial College of London* informed about a study in cooperation with a Canadian Institute: they investige seasonal variations in asthma hospitalisations in the UK, Canada and other countries, in particular, the relation of exacerabation peaks to return to school dates and deprivation and relationship with routinely collected information on respiratory infectious diseases. The funding was organised by the Canadian collaborator, and relies heavily on a research grant from pharmaceutical industry. Another study of this institution in cooperation with the *University of Aberdeen* refers to an epidemiological comparison of consultation rates in primary care for asthma and allergic diseases to generate hypotheses about environmental and maturational influences on asthma, particularly in relation to gender differences. The costs are shared by a British public organization and the universities.

Projects on the interaction betwen genes and the environment

Researchers of the *Belgique University of Leuven* informed about their ongoing FONIA project, a prospective study including 107 children to evaluate the in-vitro T-cell and APC

cytokine production in response to allergens and/or polyclonal stimulation, at birth and 3 other time points until age 6, and its relation with the development of atopy and/or allergic asthma. The cells are also stocked for genetic analyses. Estimated costs for this project including clinical-follow up, laboratory costs and salaries amount to EUR 740,000. The study started in 2001 and will end in 2008. 70% of total costs are borne by 2 Belgique funds for scientific research, about 0,5% is contributed by pharmaceutical industry, and for the rest sponsors have yet to be found.

About six years ago, investigators of the *Copenhagen University Hospital* started a longitudinal birth-cohort study with children of asthmatic mothers to explore the relationship between genetic, environmental and lifestyle factors in the development of atopic disease. This 6-year-study raised total costs of about EUR 500,000. The dominant support came from private Danish organizations, and minor contributions from the Danish government and pharmaceutical industry.

The EU-project PDCAAE (Prevalence and Determinants of Childhood Asthma and Allergies across Europe) has been coordinated by the *University of Ulm*. It was aimed at an assessment of the variance of childhood asthma and allergies across Europe and the relation with known and suspected risk factors within and between study centres. Cooperating institutions have been top centers of childhood asthma research in Sweden, Germany, Great Britain and Netherlands. The 4 years' contribution of the EU amounted to EUR 1 million.

The impact of feeding regimen in infancy, environmental exposures and genetic predisposition on the development of atopic diseases in children has been evaluated by the *German GSF* in cooperation with other German institutions in a longitudinal study started in 1995 and lasting until 2004/05. This project (GINI PLUS) was funded by the German Ministry of Research and other German public institutions.

The Allergy and Asthma Centre at the *Charité-Humboldt University Berlin* is involved in a number of projects focussing on the prediction and prevention of allergy and asthma including a wide range of animal experimental approaches using rat and mouse models. One of this projects is, for example, the MAS90 - Multicentre Allergy Study – which started in 1990 and is a prospective birth cohort study including newborns in 5 different German cities. Annual available funding for activities of Charité scientists in this field reaches EUR 1.5 million, of which about 30% are contributed by the university, 40% by public organizations, and 30% by pharmazeutical industry.

In Hungary, researchers of the *Semmelweis Medical University Budapest* have been studying gene polymorphisms in asthmatic children and the role of gene-environmental interactions. They are also establishing a Hungarian biobank. The funding amounts to EUR 300,000 for 3 years and is borne by the Hungarian National Scientific Research Fund.

The Karelian Allergy Study (KARA) of the Finnish Lung Health Association examines possible differences in allergic phenotype and genotype between Finnish and Russian school children, and tries to explore the relative impact of genes versus environmental factors in the development of atopic disease in these two populations. 56% of the estimated total costs of EUR 300,000 are contributed by the Academy of Finland, funding of the remaining 44% stilll unresolved.

The *Swedish Karolinska Institute* has performed the big BAMSE-study (Stockholm Children Allergy and Environmental Prospective Birth Cohort Study) resulting in a couple of publications with a few more coming up. The Swedish researchers studied environmental risk factors in relation to genetics for allergic diseases of various severity degrees by using an interdisciplinary approach. This study was part of some EU-funded projects, and received additional support from the Swedish Environmental Protection Agency, private organizations and the university.

Researchers of the *University of Aberdeen* perform a laboratory study to test associatons and allelic transmission of candidate polymorphisms on the Chemokine pathway for asthma and related phenotypes of atopy (allergy), lung function, and bronchial hyperresponsiveness. In this study, some environmental exposure data, such as tobacco smoke exposure or other features of the home environment, are also taken into consideration. The funding of totally 80,000 Euro was received via a scholarship of the government of Saudi Arabia (80%) and pharmaceutical industry (20%). In a clinical study of this institution, the hypothesis that dietary exposures in pregnancy and early childhood contribute to the expression of childhood asthma is tested. Plans are being made to extend this study to relevant genetic candidates, particularly to functional polymorphisms on the antioxidant pathway. A cost contribution of EUR 200,000 was received from UK's National Asthma Campaign.

The *David Hide Asthma and Allergy Research Centre* at the Isle of Wight established a birth cohort in 1989 to study the natural history of asthma and allergic diseases and to evaluate the impact of environmental risk factors. Genetic studies are being carried out with a current foucs on IL13 polymorphisms. The next planned follow-up of these children is at the age of 16. The 10 years' follow-up was funded by UK's National Asthma Campaign, the funding for the 16 years' follow-up is yet unresolved.

Conclusions

There seems to be unprecedented interest in the research of paediatric asthma at all levels, and a considerable number of European investigators have been trying to explore the fundamental causes of asthma. The top research institutions are located in Great Britain, Germany and Scandinavian countries, but there are also some highly efficient smaller groups in the new EU25 countries.

With the exception of UK's National Asthma Campaign, and a few other private initiatives in Scandinavian countries, funding of this type of research relies heavily on public sources. However, the contribution of pharmaceutical industry is also remarkable, considering the fact that discovering the causes of asthma is not their primary interest unless these findings can be used for the development of new therapeutic agents.

Increased cooperation between research groups on a European level will certainly allow better selection of bigger study populations and pool common experience and resources of basic and clinical scientists.

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References

1. Allen M et al (2003) Positional cloning of a novel gene influencing asthma from chromosome 2q14. Nat Genet 35: 258-263
2. Almqvist C et al (2003) Direct and indirect exposure to pets – risk of sensitization and asthma at 4 years in a birth cohort. Clin Exp Allergy 33: 1190-1197
3. Almqvist C et al (2003) Heredity, pet ownership, and confounding control in a population-based birth cohort. J Allergy Clin Immunol 111: 800-806
4. Arshad SH et al (2003) Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: a randomised controlled study. Thorax 58: 489-493
5. Bager P et al (2003) Smallpox vaccination and risk of allergy and asthma. J Allergy Clin Immunol 111: 1227-1231
6. Bager P et al (2003) Age at bacille Calmette-Guerin vaccination and risk of allergy and asthma. Clin Exp Allergy 33: 1512-1517
7. Bege B et al (2003) Polymorphisms in the interleukin-4 and interleukon-4 receptor alpha chain genes confer susceptibility to asthma and atopy in a Caucasian population. Clin Exp Allergy 33: 1111-1117
8. Bernard A et al (2003) Lung hyperpermeability and asthma prevalence in schoolchildren: unexpected associations with the attendance at indoor chlorinated swimming pools. Occup Environ Med 60: 385-394
9. Bernsen RM et al (2003) Birth order and sibship size as independent risk factors for asthma, allergy, and eczema. Pediatr Allergy Immunol 14: 464-469
10. Bogacka E et al (2003) Allergy to mould allergens as a risk factor for bronchial asthma in patients suffering from allergic rhinitis. Pol Merkurisusz Lek 14: 388-392
11. Bornehag CG et al (2003) Pet-keeping in early childhood and airway, nose and skin symptoms later in life. Allergy 58: 939-944
12. Bottcher MF et al (2003) Allergen-induced cytokine secretion in atopic and non-atopic asthmatic children. Pediatr Allergy Immunol 14: 345-350
13. Braback L et al (2004) Trends in asthma, allergic rhinitis and eczema among Swedish conscripts from farming and non-farming environments. A nationwide study over three decades. Clin Exp Allergy 34: 38-43
14. Brown V et al (2003) T cell cytokine profiles in childhood asthma. Thorax 58: 311-316

15. Burr ML et al (2003) Pollen counts in relation to the prevalence of allergic rhinoconjunctivitis, asthma and atopic eczema in the International Study of Asthma and Allergies in Childhood (ISAAC). Clin Exp Allergy 33: 1675-1680
16. Calvani M et al (2004) Infectious and uterus related complications during pregnancy and development of atopic and nonatopic asthma in children. Allergy 59: 99-106
17. Cesaroni G et al (2003) Individual and area-based indicators of socioeconomic status and childhood asthma. Eur Respir J 22: 619-624
18. Chauhan AJ et al (2003) Personal exposure to nitrogen dioxide (NO2) and the severity of virus-induced asthma in children. Lancet 361: 1939-1944
19. Child F et al (2003) The association of maternal but not paternal genetic variation in GSTP1 with asthma phenotypes in children. Respir Med 97: 1247-1256
20. Child F et al (2003) Correction of bronchial challenge data for age and size may affect the results of genetic association studies in children. Pediatr Allergy Immunol 14: 193-200
21. Cullinan P et al (2004) Early prescriptions of antibodies and the risk of allergic disease in adults: a cohort study. Thorax 59: 11-15
22. Diez U et al (2003) Redecoration of apartments promotes obstructive bronchitis in atopy risk infants – results of the LARS study. Int J Hyg Environ Health 206: 173-179
23. von Ehrenstein OS et al (2004) Alpha1 antitrypsin and the prevalence and severity of asthma. Arch Dis Child 89: 230-231
24. Farchi S et al (2003) Dietary factors associated with wheezing and allergic rhinitis in children. Eur Respir J 22: 772-780
25. Fritz GJ et al (2004) Asthmatic disease among urban preschoolers: an observational study. Int J Hyg Environ Health 207: 23-30
26. Frye C et al (2003) Maternal oral contraceptive use and atopic diseases in the offspring. Allergy 58: 229-232
27. Gruber C et al (2003) Transient suppression of atopy in early childhood is associated with high vaccination coverage. Pediatrics 111: e282-e288
28. Gustafsson D et al (2004) Effect of indoor environmental factors on development of atopic symptoms in children followed up to 4 years of age. Paediatr Perinat Epidemiol 18: 17-25
29. Hagendorens MM et al (2003) Differences in circulating dentritic cell subtypes in cord blood and peripheral blood of healthy and allergic children. Clin Exp Allergy 33: 633-639

30. Halasz A et al (2003) Relationship between the tumor necrosis factor system and the serum interleukin-4, interleukin-5, interleukin-8, eosinophil cationic protein, and immunoglobulin E levels in the bronchial hyperreactivity of adults and their children. Allergy Asthma Proc 24: 111-118
31. Heinzmann A et al (2003) Association of uteroglobulin-related protein 1 with bronchial asthma. Int Arch Allergy Immunol 131: 291-295
32. Heinzmann A et al (2003) Association study of the IL13 variant Arg110Gln in atopic diseases and juvenile idiopathic arthritis. J Allergy Clin Immunol 112: 735-739
33. Heinzmann A et al (2003) Promoter polymorphisms of the CD14 gene are not associated with bronchial asthma in Caucasian children. Eur J Immunogenet 30: 345-348
34. Hesselmar B et al (2003) High-dose exposure to cat is associated with clinical tolerance – a modified Th2 immune response? Clin Exp Allergy 33: 1681-1685
35. Hunter PR et al (2003) The prevalence of self-reported symptoms of respiratory disease and community belief about the severity of pollution from various sources. Int J Environ Health Res 13: 227-238
36. Hyvarinen A et al (2003) Microbial exposure and mold-specific serum IgG levels among children with respiratory symptoms in 2 school buildings. Arch Environ Health 58: 275-283
37. Ising H et al (2003) Respiratory and dermatological diseases in children with long-term exposure to road traffic immissions. Noise Health 5: 41-50
38. Jaakkola JJ et al (2004) Maternal smoking in pregnancy, fetal development, and childhood asthma. Am J Public Health 94: 136-140
39. Jones AP et al (2003) Early life exposures and the prevalence of atopic disorders in a sample of school-age infants. Monaldi Arch Chest Dis 59: 38-43
40. Juntti H et al (2003) Association of an ealry respiratory syncytial virus infection and atopic allergy. Allergy 58: 878-884
41. Kabesch M et al (2003) Association between polymorphisms in caspase recruitment domain containing protein 15 and allergy in two German populations. J Allergy Clin Immunol 111: 813-817
42. Kabesch M et al (2003) A complete screening of the IL4 gene: novel polymorphisms and their association with asthma and IgE in childhood. J Allergy Clin Immunol 112: 893-898
43. Kihlstrom A et al (2003) Exposure to high doses of birch pollen during pregancy, and risk of sensitization and atopic disease in the child. Allergy 58: 871-877

44. Koppelman GH et al (2003) Sibling effect on atopy in children of patients with asthma. Clin Exp Allergy 33: 170-175
45. Kramer U et al (2004) The effect of environmental tobacco smoke on eczema and allergic sensitization in children. Br J Dermatol 150: 111-118
46. Kurukulaaratchy RJ et al (2004) Does environment mediate earlier onset of the persistent childhood asthma phenotype? Pediatrics 113: 345-350
47. Longhini E et al (2004) Lung function and methacholine responsiveness among adolescents in an air-polluted area. Respiration 71: 51-59
48. Mai XM et al (2003) High body mass index, asthma, and allergy in Swedish schoolchildren participating in the International Study of Asthma and Allergies in Childhood: Phase II. Acta Paediatr 92: 1144-1148
49. Mai EM et al (2003) Asthma, lung function and allergy in 12-year-old children with very low birth weight: a prospective study. Pediatr Allergy Immunol 14: 184-192
50. Moffatt S et al (2003) „It was'nt the plague we expected." Parents' perceptions of the health and environmental impact of opencast coal mining. Soc Sci Med 57: 437-451
51. Migliaccio C et al (2003) No linkage or association of five polymorphisms in the interleukin-4 receptor alpha gene with atopic asthma in Italian families. Eur J Immunogenet 30: 349-353
52. Nagy A et al (2003) The development of asthma in children infected with Chlamydia pneumoniae is dependent on the modifying effect of mannose-binding lectin. J Allergy Clin Immunol 112: 729-734
53. Neto AS et al (2003) Risk factors for the nasopharyngeal carriage of respiratory pathogens by Portuguese children: phenotype and antimicrobial susceptibility of Haemophilus influenzae and Streptococcus pneumoniae. Microb Drug Resist 9: 99-108
54. Nicolai T et al (2003) Urban traffic and pollutant exposure related to respiratory outcomes and atopy in a large sample of children. Eur Resp J 21: 956-963
55. Nilsson L et al (2003) Allergic disease at the age of 7 years after pertussis vaccination in infancy: results from the follow-up of a randomized controlled trial of 3 vaccines. Arch Pediatr Adolesc Med 157: 1184-1189
56. Oberle D et al (2003) Childhood asthma and continuous exposure to cats since the first year of life with cats allowed in the child's bedroom. Allergy 58: 1033-1036
57. Rushton L et al (2003) Estimation of the impact on children's health of environmental tobacco smoke in England and Wales. J R Soc Health 123: 175-180

58. Sayers I et al (2003) Promoter polymorphism in the 5-lipoxygenase (ALOX5) and 5-lipoxygenase-activating protein (ALOX5AP) genes and asthma susceptibility in a Caucasian population. Clin Exp Allergy 33: 1103-1110
59. Sayers I et al (2003) Allelic association and functional studies of promoter polymorphism in the leukotriene C4 synthase gene (LTC4S) in asthma. Thorax 58: 417-424
60. Schuller et al (2003) The role of the IKAP gene polymorphisms in atopic diseases in the middle European population. J Hum Genet 48: 300-304
61. Sengler C et al (2003) Clara cell protein 16 (CC16) gene polymorphism influences the degree of airway responsiveness in asthmatic children. J Allergy Clin Immunol 111: 515-519
62. Sengler C et al (2003) Evaluation of the CD14 C-159 T polymorphism in the German Multicenter Allergy Study cohort. Clin Exp Allergy 33: 166-169
63. Sidorchuk A et al (2003) Epstein-Barr virus infection is not associated with development of allergy in children. Pediatr Infect Dis J 22: 642-647
64. Siroux V et al (2003) Relationships of allergic sensitization, total immunoglobulin E and blood eosinophils to asthma severity in children of the EGEA study. Clin Exp Allergy 33: 746-751
65. Srivastava P et al (2003) Association of CCR5Delta32 with reduced risk of childhood but not adult asthma. Thorax 58: 222-226
66. van Strien RT et al (2003) Mattress encasings and mite allergen levels in the Prevention and Incidence of Asthma and Mite Allergy study. Clin Exp Allergy 33: 490-495
67. Strumylaite L et al (2003) Atmosphere air pollution and health of Kaunas children. Medicina (Kaunas) 39: 83-89
68. Sunyer J et al (2003) Respiratory effects of sulphur dioxide: a hierarchical multicity analysis in the APHEA 2 study. Occup Environ Med 60: e2
69. Tobias A et al (2003) Short term effects of airborne pollen concentrations on asthma epidemic. Thorax 58: 708-710
70. Wickman M et al (2003) Strategies for preventing wheezing and asthma in small children. Allergy 58: 742-747
71. Wijga AH (2003) Association of consumption of products containing milk fat with reduced asthma risk in pre-school children: the PIAMA birth cohort study.
72. Xu B et al (2003) Maternal sex hormones in early pregnancy and asthma among offspring: a case-control study. J Allergy Clin Immunol 112: 1101-1104
73. Zejda JE et al (2003) Risk factors for asthma in school children – results of a seven-year follow-up. Cent Eur J Public Health 11: 149-154

74. Zhang Y et al (2003) Positional cloning of a quantitative trait locus on chromosome 13q14 that influences immunoglobulin E levels and asthma. Nat Genet 34: 181-186
75. Zmirou D et al (2004) Traffic related air pollution and incidence of childhood asthma: results of the Vesta case-control study.

Table 1. Publications of EU25 investigators between 2003-01-01 and 2004-02-28, including original reports and review articles, excluding case-reports, editorials and letters/comments

Country	Number of publications addressing asthma in children	Number of publications addressing genetic and/or environmental factors in children with asthma
Austria	4	1
Belgium	8	2
Cyprus	0	0
Czech Republic	1	1
Denmark	16	2
Estonia	0	0
Finland	13	4
France	45	12
Germany	55	18
Greece	5	1
Hungary	5	2
Ireland	2	0
Italy	47	7
Latvia	0	0
Lithuania	1	1
Luxembourg	0	0
Malta	0	0
Netherlands	27	5
Poland	10	3
Portugal	2	1
Slovakia	2	0
Slovenia	0	0
Spain	14	2
Sweden	25	13
United Kingdom	107	29
Total number	*389*	*104*