
The Copenhagen Prospective Study on Asthma in Childhood (COPSAC): design, rationale, and baseline data from a longitudinal birth cohort study

Hans Bisgaard, MD, DMSci

Background: The atopic diseases asthma, atopic dermatitis, and allergic rhinitis are the most common chronic diseases in children, and their prevalence has increased recently in industrialized nations. Little is known about the genetic-environmental interaction factors driving such proliferation.

Objective: To investigate the relationships among genetic, environmental, and lifestyle factors in the development of atopic diseases in high-risk children with the aim of developing evidence-based prevention strategies.

Methods: The Copenhagen Prospective Study on Asthma in Childhood is a single-center, birth cohort study of children of asthmatic mothers. Objective assessments begin at birth, with scheduled visits every 6 months and when acute symptoms manifest. Clinical outcomes comprise preasthma, asthma, atopic dermatitis, allergic rhinitis, allergy, lung function, and bronchial responsiveness. Exposure assessments comprise respiratory, intestinal, and skin microbiology; the child's diet; indoor and outdoor air quality; allergens; and indicators of lifestyle. Genetic characteristics of probands and parents are evaluated. Quality assurance follows Good Clinical Practice guidelines.

Results: Four hundred eleven infants of asthmatic mothers were enrolled at the age of 1 month. The children were born between August 2, 1998, and December 28, 2001. Compared with the Copenhagen population, mothers of the cohort population were less likely to have given natural childbirth. The households were slightly less affluent, with fewer children and fewer pets. Whites may be overrepresented. At age 2 years, 93% of the infants were still actively participating in the cohort.

Conclusions: This longitudinal birth cohort study of high-risk Danish infants consists of objective phenotyping, detailed information on exposure, high data quality, and a high participant retention rate.

Ann Allergy Asthma Immunol. 2004;93:381–389.

INTRODUCTION

The atopic diseases asthma, atopic dermatitis (AD), and allergic rhinitis (AR) are the most common chronic pediatric illnesses, with estimated prevalences in young children in northern Europe of approximately 8%,¹ approximately 11%,² and more than 15%,³ respectively. However, estimating the true prevalence of these diseases is complicated by age-dependent phenotypes, the lack of standardized definitions, and the effects of culture and geography. Their prevalence has increased in industrialized nations in recent decades,^{4–6} likely owing to as-yet-unidentified changes in environmental and lifestyle factors that interact with genetic determinants because prevalence seems to coincide with the affluence of the population^{7,8} and varies between populations of similar ethnic origins living in different regions.⁹ Most cases of atopic disease are diagnosed in the first years of life, and outcomes in adult asthma seem to be determined in early childhood.¹⁰

The Copenhagen Prospective Study on Asthma in Childhood (COPSAC) is a birth cohort study designed to assess the genetic-environmental interaction in high-risk infants and young children, with the aim of identifying early-life exposures that can be modified to prevent the development of atopic diseases. This article reviews the design, methods, and rationale of this cohort study. In addition, baseline data and whether they are representative of the general population in the Copenhagen area are presented together with subject recruitment and retention during the first 2 years of the children's lives.

METHODS

COPSAC is a single-center, prospective birth cohort study. The study is conducted in accordance with the Declaration of Helsinki and was approved by the Copenhagen Ethics Committee (KF01-289/96) and the Danish Data Protection Agency (1996-1200-360).

Screening for Pregnant Asthmatic Women

The Danish National Birth Cohort Study¹¹ of approximately 100,000 pregnant women allowed targeted invitation of pregnant women. Women from the greater Copenhagen area who reported a history of asthma were invited to receive further

Department of Pediatrics, Copenhagen University Hospital, Copenhagen, Denmark.

Received for publication May 6, 2004.

Accepted for publication in revised form June 7, 2004.

information about the COPSAC. Also, we invited pregnant women with asthma who were attending prenatal clinics. Women who indicated an interest in the study were interviewed by telephone regarding eligibility criteria, including fluency in Danish, a physician's diagnosis of asthma after the age of 7 years, and a history of daily treatment with inhaled β_2 -agonists or glucocorticoids for a minimum of 2 weeks during 2 seasons or continuously for 1 year. Eligible women subsequently received information by mail. Women reconfirming an interest were invited to the COPSAC Clinical Research Unit (CRU) for detailed information. Women who provided informed consent received guidance on cord blood sampling.

Enrollment of Infants

Infants of consenting mothers were enrolled in the cohort at the CRU visit 1 month after birth, excluding infants with a severe congenital anomaly, a gestational age younger than 36 weeks, a need for mechanical ventilation, or a lower respiratory tract infection.

Clinical Assessments

Children attend the CRU at 1 month of age, every 6 months until the age of 7 years. The scheduled clinical investigations are reviewed in Table 1. Children with acute troublesome lung symptoms (TLS) or acute dermatitis complaints are seen

Table 1. Scheduled Investigations of the COPSAC Birth Cohort

Outcome	Cord blood	1 mo	6 mo	1 y	2 y	3 y	4 y	5 y	6 y	Acute care visits
Lung function										
Baseline sRaw		X			X	X	X	X	X	
Postbronchodilator sRaw						X		X		
Bronchial hyperresponsiveness		X					X		X	
Upper airways										
Nasal airway resistance and responsiveness								X		
Nasal eosinophils								X		
Tympanometry					X			X		
Microbiology										
Fecal bacteria		X		X						
Skin bacteria		X		X						X
Airway virus				X						X
Airway bacteria		X		X						X
Inflammatory markers										
Exhaled nitric oxide		X						X	X	
Urine cysteinyl leukotrienes and eosinophil protein		X	X	X		X	X		X	
Blood eosinophils			X	X			X		X	
Nasal eosinophils								X		
Immunology										
Skin test			X	X			X		X	
Plasma and serum	X		X	X			X		X	
Mononuclear cells			X							
Indoor air quality										
Cotinine (hair, serum, urine)	X	X	X	X						
PM _{2.5}			X	X						
Nitrogen oxides			X	X						
Volatile organic compounds			X	X						
Humidity and temperature				X						
Allergens in beddings				X						
Diet										
Mother's milk		X								
Introduction of solid foods			X	X						
Growth										
Length/height		X	X	X	X	X	X	X	X	
Bone density						X			X	

Abbreviations: COPSAC, Copenhagen Prospective Study on Asthma in Childhood; PM_{2.5}, particulate matter measuring less than 2.5 μm in aerodynamic diameter; sRaw, specific airway resistance.

at the clinic by physicians employed at the CRU who are permanently on call.

History. Information is obtained on socioeconomic indicators, prenatal exposures, complications during pregnancy, and the child's delivery. At every visit, information is obtained on diseases, vaccinations, and the use of any medications. Any TLS (as composite dichotomized scores [yes/no]) and the use of inhaled β_2 -agonists are prospectively recorded in a diary for the first 6 years of life.

Physical examination and evaluation of growth. A full physical examination is performed at each scheduled clinic visit. Growth is measured until the age of 2½ years using an infantometer (Kiddimeter; Raven Equipment Ltd, Dunmow, Essex, England).¹² From 2½ years, height is measured using a stadiometer (Harpender; Holtain Ltd, Crymych, Dyfed, Wales).¹² Bone density and structure are evaluated at 3 and 6 years of age using ultrasound absorptiometry (IGEA, Carpi, Italy).¹³

Blood sampling and inflammatory and immunologic markers. Serum and plasma specimens are collected and stored at -80°C from cord blood and blood samples taken at regular intervals beginning at the age of 6 months (Table 1). Mononuclear cells are isolated at 6 months of age and stored in liquid nitrogen. Urine samples are obtained at the age of 1 month and annually thereafter for measurement of eicosanoids and markers of eosinophilic granulocytes. Exhaled nitric oxide is measured at 1 month of age using an offline technique and starting at the age of 5 years using an online technique.¹⁴

Genetics and family history. DNA from children and parents is purified using the QIAamp DNA Blood Maxi Kit (Qiagen Inc, Valencia, CA) and is stored at -80°C . Spirometry and bronchial responsiveness to methacholine are obtained in participating mothers, and allergy to common inhalant allergens is determined using quantitative ImmunoCAP (Pharmacia Diagnostics AB, Uppsala, Sweden)¹⁵ in both parents.

Lung function. Lung function is measured at the age of 1 month using the raised volume rapid thoracoabdominal compression technique.¹⁶ Beginning at the age of 2 years, specific airway resistance (sRaw) is measured yearly using whole-body plethysmography.¹⁷ Spirometry is obtained beginning at the age of 5 years. Postbronchodilator sRaw is measured at 3 and 5 years of age.¹⁸ Bronchial responsiveness is measured at the age of 1 month by methacholine challenge and raised volume rapid thoracoabdominal compression measurements. At the ages of 4 and 6 years, bronchial responsiveness is evaluated by cold dry-air hyperventilation¹⁹ and sRaw measurements. At the age of 7 years, bronchial responsiveness is evaluated by exercise on a treadmill breathing dry air.

Preasthma and asthma. Preasthma is the term used to describe recurrent episodes of TLS. Asthma is diagnosed based on preasthma and response and subsequent relapse to a 3-month trial of inhaled corticosteroids. Differential diagnoses are excluded by radiography and sweat testing.

Atopic dermatitis, Allergic rhinitis and allergy. The diagnosis of AD is based on the criteria of Hanifin and Rajka.²⁰ The severity of AD is graded using the SCORAD index.²¹ Allergic rhinitis is diagnosed from persistent irritative or congestive symptoms in the absence of a common cold.²² Nasal patency is measured at the ages of 5 and 7 years using acoustic rhinometry,²³ including response to epinephrine. An eosinophil count in a sample of nasal mucosa is done at the age of 5 years. Tympanometry is performed at the ages of 2 and 5 years. Skin prick tests²⁴ and specific IgE by ImmunoCAP¹⁵ to common aeroallergens and food allergens are performed at the ages of 6 months, 18 months, 4 years, and 6 years.

Nested Interventional Study: Preasthma Control

The Preasthma Control study examines whether early intermittent treatment with inhaled corticosteroids prevents or delays the recurrence of TLS and asthma in early childhood. All COPSAC children are randomly preassigned to receive either budesonide, 400 μg , or placebo for 14 days at any episode of 3 consecutive days of TLS until the age of 3 years or until a diagnosis of asthma is considered.

Environmental and Lifestyle Assessments

Microbiology. Respiratory bacteria and viruses are isolated from laryngeal and nasal secretions in asymptomatic children during infancy and at every episode (3 consecutive days) of TLS during the first 3 years of life. Bacterial species are cultured. The respiratory viruses as well as *Mycoplasma pneumoniae*, *Ureaplasma urealyticum*, and *Chlamydia pneumoniae* are identified by reverse transcriptase-polymerase chain reaction.²⁵ Intestinal flora is cultured from stool samples taken during infancy, and constituent aerobic and anaerobic bacteria are identified using nucleic acid-based techniques. *Staphylococcus aureus* and streptococcal species are cultured during infancy from the nasal cavity and perineum and from any skin lesions suggestive of AD.

Diet. Mature postcolostrum breast milk is collected 1 month post partum to measure fatty acids, dioxins, estrogen, and endocrine disruptors. Information about the child's diet in the first year of life is obtained prospectively using a nutritional questionnaire.

Indoor and outdoor air quality. Environmental tobacco smoke exposure is evaluated by cotinine levels in samples of cord blood, serum, urine, and the child's hair.²⁶ Fine-particle ($<2.5\ \mu\text{m}$) particulate matter concentration is measured using a cyclone²⁷ in the child's bedroom during 2 periods in the first years of life. Nitrogen oxide levels are measured using Palmes tubes²⁸ and volatile organic compounds are measured using Radiello tubes²⁹ in the bedroom for 10 weeks on 2 to 3 occasions during the first years of life. Indoor humidity and temperature in the child's bedroom are logged regularly during the autumn months using a HOBO H8 RH/Temp Logger (Onset Computer, Bourne, MA). Allergens are analyzed in dust samples from the child's bed. Indicators of outdoor air quality (nitrogen dioxide, sulfur dioxide, and ozone) are

monitored daily at central sites around Copenhagen. Daily counts of pollen and fungal spores are available.

Data Management

Data collection is in accordance with Good Clinical Practice guidelines. Patient diary cards are entered into the study database. History is based on personal interview, with online data entry. Objective measurements are entered online.

The database is built in Oracle on a Novel SQL server (Oracle Corp, Redwood Shores, CA). Database tools are used to schedule patient visits and tests based on the study protocol and to notify the investigators about upcoming visits and missing data. Data are monitored by external data monitors. Source data verification and a plausibility check of a pre-defined range and outliers are executed. An audit trail in the database documents any editing and changes of the data by creating a copy of the current record together with information about who made the change, when, and why. After source validation, these areas of the database are locked and become inaccessible for further editing. Diagnoses are coded according to the *International Classification of Diseases, 10th Revision*, by qualified physicians employed at the CRU.

Statistical Analyses

Similarity between the COPSAC sample and the population in Copenhagen is tested using large-sample proportion tests and χ^2 goodness-of-fit tests.

RESULTS

Of 1,476 pregnant women reporting a history of asthma and interest in the study, 798 (54%) were considered to be asthmatic after a telephone interview. Of these 798 women, 548 visited the CRU to receive detailed information, and mothers of 452 infants consented to participation. Before enrollment, 2 infants were excluded owing to congenital diseases (heart disease and microcephalia), and 39 infants failed to attend the enrollment visit 1 month after birth. Thus, 411 infants of 394 mothers (9 pairs of twins and 8 siblings) were enrolled in the cohort.

The baseline characteristics of the COPSAC cohort are compared with the characteristics of the general population in Copenhagen in Table 2. Ninety-three percent of the cohort lived in urban areas at birth (Fig 1). Compared with the population of greater Copenhagen, mothers of the cohort were less likely to have given natural childbirth. Smoking among mothers was not significantly different from that in the reference population. The fathers were younger, and the households were slightly less affluent, with fewer children and fewer pets.

Fourteen children (3.4%) left the study in the first year of life (2 families relocated, 1 child died of sudden infant death syndrome, 11 families withdrew owing to lack of time) and 13 children (3.2%) left in the second year of life (3 families relocated, 8 families withdrew owing to lack of time, and 2 families withdrew dissatisfied with the investigation). Thus, 384 (93.4%) of the 411 participating children have been followed up to the age of 2 years.

DISCUSSION

The COPSAC is a birth cohort study of the development of atopic disease in children with a maternal history of asthma. The first goal is to identify early-life exposures that can be modified to prevent or limit the development of such diseases. The second objective is to identify early predictors of disease propensity to enable targeting of prevention strategies based on proper risk evaluation. The third objective is to examine whether early therapeutic interventions may slow the progression from preasthma to asthma.

Study Design

The enrollment of 411 infants was completed in slightly more than 3 years. A national birth cohort study of approximately 100,000 pregnant women helped prescreening for asthmatic mothers. Nearly half of the women who achieved the entry criteria eventually declined enrollment, with one of the main reasons being the requirements of the comprehensive test program and particularly the need to evaluate infant lung function during sedation. Similar rates of refusal are reported in other long-term interventional cohort studies.^{30,31}

Compared with the Copenhagen population, mothers of the cohort were less likely to have given natural childbirth. Smoking among mothers was not significantly different from that in the reference population. The fathers were younger, and the households were slightly less affluent, with fewer children and fewer pets. Whites may be overrepresented, although no official data exist for Copenhagen. This apparent difference may be due to the requirement for fluency in Danish.

Adherence to the study program was good. Ninety-eight percent of the cohort completed testing of lung function and bronchial responsiveness during sedation at 1 month of age. Ninety-three percent of the cohort completed the first 2 study years, and adherence remained good and data completeness high, probably owing to the detailed information given to participants before entering the study, the increased risk of atopic diseases in the children, and the formation of a dedicated CRU catering only to the participating children.

The COPSAC emphasizes objective phenotyping with repeated early lung function measurements and prospective daily diary cards together with interviews and examinations by trained physicians employed at the CRU. The children are seen at 6-month intervals and whenever an acute episode of skin or airway symptoms arises. The diagnosis and day-to-day management of any airway or skin problems is controlled by the physicians employed at the CRU, not by the family physician. This reduces the risk of misclassification of symptoms because of the influence of the prevailing diagnostic criteria and treatment traditions in the medical community. This reduced risk of misclassification is of particular importance in the clinical evaluation of disorders such as recurrent wheeze, asthma, AD, and AR in young children, where between-observer variation is significant.³²⁻³⁴ Asthma diagnosis and the treatment of lung symptoms are based on a rigid treatment algorithm. The COPSAC is a single-center study

Table 2. Demographics and Anthropometrics Comparison of the COPSAC Cohort Sample and the General Population of Greater Copenhagen, Year 2000

	COPSAC	Greater Copenhagen	P value
Population, No.		1.796 million*	
Newborns; gestational age >35 weeks, No.	411	23,030/y†	–
Child			
Birthday, range (mean)	August 2, 1998–December 29, 2001 (October 13, 2000)	–	–
Age distribution, SD, y	0.8	–	–
Boys, %	49.4	51.5†	NS
Twins, %	9 pairs	1.5†	NS
Whites, No.‡	397/411	NA	–
Birth weight, mean (SD), g	3.517 (0.520)	3.555 (0.528)†	NS
Birth length, mean (SD), cm	52.3 (2.3)	52.3 (2.4)†	NS
Gestational age (born ≥35 weeks), mean (SD)	40 (2)	40 (1.5)†	NS
Delivery			
Born at maternity clinic, % (No.)	>99 (410)	99.5†	NS
Natural, %	66	76†	
Sectio, %	21	14†	<.001
Extraction and forceps, %	13	10†	
Apgar score at 5 min, mean (SD)	9.9 (0.6)	9.9 (0.6)†	NS
Mother (n = 394)			
Age at birth of proband, mean (SD), y	30.0 (5)	30.4 (5)†	NS
Atopic dermatitis history, %	46	NA	–
Allergic rhinitis history, %	73	NA	–
Smoking during pregnancy, %			
Nonsmoker§	84	81†	
<5 cigarettes per day	4	7†	.06
≥5 cigarettes per day	12	12†	
Alcohol use during the second trimester, >3 times per week, %	1	NA	–
Father (n = 388)			
Age at birth of proband, mean (SD), y	32.1 (5)	33.1 (5.8)†	.004
Asthma history, %	15	14 ⁶⁵	–
Allergic rhinitis history, %	30	32 ⁶⁶	–
Household			
Income, mean (SD), Danish kroner	490,613 (203,164)	514,414	.002
Mother without occupation, %	19	21*	NS
Older children in household, %			
0	64	43*	<.001
1	24	39*	
2	8	13*	
≥3	3	5*	
Urban living, %	93.6	96.3	<.001
Living in greater Copenhagen, %	88	100	–
Furred pets in the house >180 d/y, %	23	34¶	<.001

Abbreviations: COPSAC, Copenhagen Prospective Study on Asthma; NA, not available; NS, not significant ($P > .01$).

* Data are from <http://www.statistikbanken.dk>.

† Data are from National Board of Health: data on newborns with gestational age older than 35 weeks.

‡ At least half of the ancestors are of the white race.

§ Includes women who stopped smoking during pregnancy.

|| Data are from Statistics Denmark: families with children.

¶ Data are from The Gallup Organisation: families in greater Copenhagen with children aged 1 to 5 years.

that ensures consistency in procedures, definitions of conditions, and data capture methods. Data management and quality control procedures are rigorous, including external mon-

itoring and prospective, online data collection into a dedicated database, with an audit trail and locking of data after source data verification.

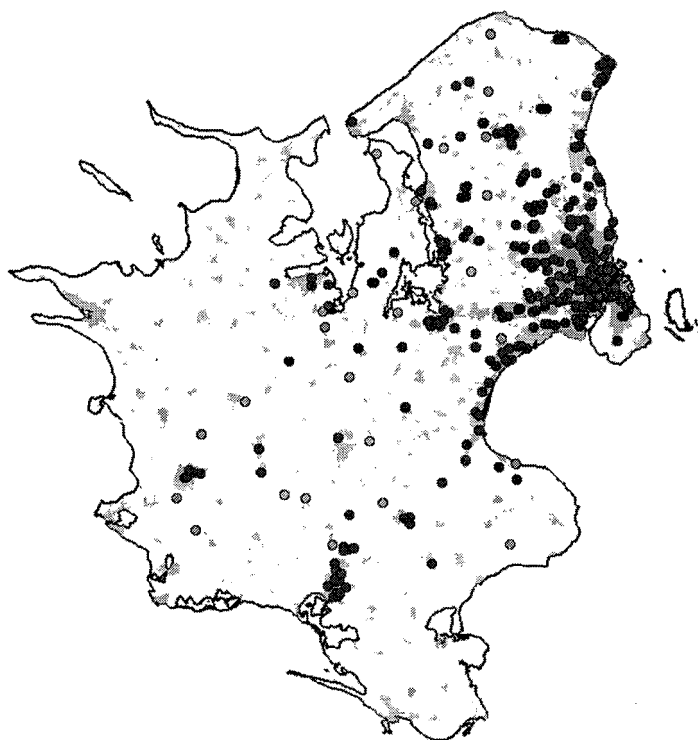


Figure 1. Geographic spread of the Copenhagen Prospective Study on Asthma in Childhood cohort at birth. Each dot indicates 1 infant. Urbanized areas are indicated in gray.

Such a comprehensive and invasive study program and meticulous data collection performed at a single center limit the overall size feasible for the study. In addition, this study may not be ethical in an unselected population. We, therefore, chose to generate hypotheses in this high-yield population of mothers with a history of asthma to increase the power of the study. This selection restricts how the findings may be generalized, and validation in unselected populations may be needed. The ethics and acceptability of this study program are currently studied through qualitative interviews of selected subgroups.^{35,36}

Clinical Outcomes

Atopic diseases consist of several subtypes with different presentations throughout life. The COPSAC provides prospective, longitudinal, long-term follow-up on the spectrum and severities of atopic diseases. Diagnosis and monitoring comprise preasthma, asthma, AD, AR, lung function, bronchial responsiveness, allergy, and inflammatory markers. Preasthma is classified as recurrent episodes (3 consecutive days) of TLS. Asthma is defined pragmatically as patients with preasthma who improve with standardized corticosteroid treatment followed by relapse on withdrawal of therapy after excluding differential diagnoses. Atopic dermatitis is identified and graded according to international standards^{20,21}; AR is delineated from validated standards²² supported by mea-

surements of nasal airway resistance, response to epinephrine, and mucosal eosinophilia. Baseline lung function is determined at 1 month of age (before any airway infections) by forced expiration in sedated infants.¹⁶ Baseline and post-bronchodilator lung function are determined annually beginning at 2 years of age by sRaw measured in awake young children using whole-body plethysmography.¹⁷ Bronchial responsiveness is determined in neonates at 1 month of age using methacholine challenge, at 4 and 6 years of age using cold dry-air hyperventilation¹⁹ and at 7 years of age using treadmill exercise tests. Inflammatory markers are measured at regular intervals.

Genetics

Samples of DNA from children and parents are available for family-based studies of genetic association in trios of parents and affected child in a single cohort, reducing the confounding effect of population stratification and ethnicity.

Exposure Evaluation

Prenatal and perinatal factors may affect the development of atopic disease. Atopic diseases cluster in families by socioeconomic level,^{37–39} probably as a surrogate measure of lifestyle factors. The COPSAC provides extensive data collected prospectively on prenatal, perinatal, and lifestyle factors.

Mothers with atopy, particularly AD, have a disturbed metabolism of the essential fatty acids⁴⁰ that may manifest in breast milk and predispose to the development of such diseases in the child. Prenatal exposure to estrogen,⁴¹ dioxin,⁴² and organochlorine compounds⁴³ has been linked to the development of allergy and asthma. Such exposure and the fatty acid composition is analyzed in the mother's milk collected in the first month post partum. The extent of breastfeeding and supplementation is recorded.

The improved hygienic conditions may have contributed to the epidemic of atopic diseases in affluent nations.^{44–46} Elaborating on this hypothesis, it has been suggested that significant changes in the intestinal flora of young infants may play a role.⁴⁷ The bacterial species colonizing the gut during infancy are evaluated in the COPSAC while adjusting for potential confounders, such as diet and antibiotic drug use.

The relation between respiratory tract infections and childhood asthma is poorly understood. Viral infections trigger asthma symptoms⁴⁸ and may even play a causative role in recurrent wheezing and possibly asthma.^{49–51} Bacteria colonize the airways shortly after birth, but their association with recurrent TLS in young children is not known. Respiratory viruses are identified and bacteria are cultured in asymptomatic infants and during acute episodes of TLS.

Staphylococcus aureus colonization of the skin is highly prevalent in children with AD. This bacterium produces a variety of toxins with superantigenic properties and suspected immunomodulatory capacity, which may contribute to disease activity.⁵² *Staphylococcus aureus* is cultured during infancy and in acute AD lesions.

Air pollution has been related to increased bronchial responsiveness⁵³ and airway symptoms, particularly during the first years of life,⁵⁴ although the association with childhood asthma remains unclear. Air pollution may also potentiate viral-induced asthma exacerbation.⁵⁵ Indoor particulate matter (<2.5 μm), nitrogen oxide, and volatile organic compounds are measured regularly in the bedrooms of the children during the first years of life, together with indoor humidity and temperature. In addition, data on outdoor pollution are available. Exposure to environmental tobacco smoke is estimated by cotinine levels in cord blood, hair, and urine samples.

Allergen exposure relates to the development of allergy, but the relation to asthma is unclear.¹ Early exposure to pets has even been suggested to protect against the development of atopic disease.⁵⁶ Inhalant allergens are analyzed in the dust samples collected from children's bedding.

Secondary Prevention

The COPSAC is evaluating the efficacy of intermittent early anti-inflammatory drug intervention in children with preasthma as a method of secondary disease prevention, as described in the "Nested Interventional Study: Preasthma Control" subsection.

Other Cohorts

Since initiation of the grand ancestor of modern long-term, longitudinal birth cohort studies in asthma—the Tucson Children's Respiratory Study—in Arizona in 1980 (N = 1,246),⁵⁷ several prospective birth cohort studies have been undertaken, including Perth, Australia (1987; N = 253)⁵⁸; Isle of Wright, England (1990; N = 1,456)⁵⁹; the Multicenter Atopy Study (MAS-90) in Germany (1990; N = 1,114)⁶⁰; BAMSE in Stockholm, Sweden (1994; N = 4,093)⁶¹; Boston, MA (1994; N = 496)⁶²; the National Asthma Campaign Manchester Asthma and Allergy Study (^{NAC}MAAS) in England (1995; N = 1,085)⁶³; the Prevention and Incidence of Asthma and Mite Allergy birth cohort study (PIAMA) in the Netherlands (1996; N = 3,291)³⁰; the Childhood Origins of Asthma study in Wisconsin (COAST) (1998; N = 287)⁶⁴; and the COPSAC in Copenhagen (1998; N = 411).

In the COPSAC, ^{NAC}MAAS,⁶³ and PIAMA³⁰ the cohorts were recruited during the mother's pregnancy; in the other studies, the cohorts were included during the first months of life. The COPSAC, Boston,⁶² and COAST studies⁶⁴ included all high-risk infants based on the mother's asthma or parental allergy. The MAS-90,⁶⁰ ^{NAC}MAAS,⁶³ and PIAMA³⁰ consisted partly of high-risk infants and partly of a cross-sectional control group, whereas the cohorts from Tucson,⁵⁷ Perth,⁵⁸ Isle of White,⁵⁹ and BAMSE⁶¹ included unselected infants. The COPSAC is a single-center study, like most of the other cohort studies, except the multicenter trials of MAS-90⁶⁰ and PIAMA.³⁰ Interventional studies on the manipulation of allergen levels in the home are nested into the ^{NAC}MAAS⁶³ and the PIAMA.³⁰ Randomized controlled trials of early interven-

tion with inhaled corticosteroids are nested in the ^{NAC}MAAS⁶³ and the COPSAC.

The most important distinguishing factor of the COPSAC is the emphasis on objective phenotyping, including regular lung function measurements beginning in infancy. The COPSAC is the only cohort in which phenotyping is based on diary cards, regular and acute care visits to the CRU, and control of diagnosis and treatment by the CRU as opposed to the community physician.

CONCLUSION

The COPSAC is a birth cohort study with extensive objective phenotyping and detailed information on environment and lifestyle. The data quality and rate of retention of participating children are high. It is hoped that the COPSAC will improve our understanding of the genetic-environmental interaction in the development of atopic disease in early childhood.

ACKNOWLEDGMENTS

I thank all the families participating in the COPSAC cohort for their effort and commitment; Lena Vind and Kirsten Mathisen, laboratory technicians, and Malene Stage, MSc, project coordinator, for their skillful and dedicated work; and the Steering Committee of the Danish National Birth Cohort study and the midwives at greater Copenhagen municipal hospitals for providing information to mothers about the COPSAC.

The COPSAC birth cohort is sponsored by the following funds: the Pharmacy Foundation of 1991; the Lundbeck Foundation; Ronald McDonald House Charities; the Danish Medical Research Council; Direktør, K. Gad Andersen og Hustrus Familiefond; Aage Bangs Fond; Danish Lung Association; Kai Lange og Gunhild Kai Langes Fond; Direktør, Ib Henriksens Fond; Gerda og Aage Hensch's Fond; Rosalie Petersens Fond; Hans og Nora Buchards Fond; Dagmar Marshalls Fond; Foundation of Queen Louise's Children Hospital; the Danish Hospital Foundation for Medical Research, Region of Copenhagen, the Faroe Island, and Greenland; Gangsted Fond; Højmossegård-Legatet; Fonden til Lægevidenskabens Fremme. A. P. Møller og Hustru Chastine McKinney Møllers Fond til almene Formaal; and the Danish Ministry of the Interior and Health's Research Centre for Environmental Health. The nested intervention study is sponsored by AstraZeneca. The analyses of specific IgE are sponsored by Pharmacia-Pfizer.

The participating investigators are as follows: Lotte Lolland, MD, PhD; Frederik Buchvald, MD, PhD; Liselotte Brydensholt, MD, PhD; Mette Hermansen, MD; Mette Ehmer Olesen, MD; and Signe Vahlkvist, MD.

REFERENCES

1. Lau S, Illi S, Sommerfeld C, et al; Multicentre Allergy Study Group. Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. *Lancet*. 2000; 356:1392–1397.

2. Bohme M, Svensson A, Kull I, Nordvall SL, Wahlgren CF. Clinical features of atopic dermatitis at two years of age: a prospective, population-based case-control study. *Acta Derm Venereol.* 2001;81:193–197.
3. Kulig M, Klettke U, Wahn V, Forster J, Bauer CP, Wahn U. Development of seasonal allergic rhinitis during the first 7 years of life. *J Allergy Clin Immunol.* 2000;106:832–839.
4. Taylor B, Wadsworth J, Wadsworth M, Peckham C. Changes in the reported prevalence of childhood eczema since the 1939–45 war. *Lancet.* 1984;2:1255–1257.
5. Anderson HR, Butland BK, Strachan DP. Trends in prevalence and severity of childhood asthma. *BMJ.* 1994;308:1600–1604.
6. Downs SH, Marks GB, Sporik R, Belosouva EG, Car NG, Peat JK. Continued increase in the prevalence of asthma and atopy. *Arch Dis Child.* 2001;84:20–23.
7. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet.* 1998;351:1225–1232.
8. von Mutius E, Weiland SK, Fritzsche C, Duhme H, Keil U. Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. *Lancet.* 1998;351:862–866.
9. Hjert A, Rasmussen F, Johansson M, Aberg N. Migration and atopic disorder in Swedish conscripts. *Pediatr Allergy Immunol.* 1999;10:209–215.
10. Sears MR, Greene JM, Willan AR, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med.* 2003;349:1414–1422.
11. Olsen J, Melbye M, Olsen SF, et al. The Danish National Birth Cohort: its background, structure and aim. *Scand J Public Health.* 2001;29:300–307.
12. Bisgaard H, Allen D, Milanowski J, Kalev I, Willits L, Davies P. Twelve-month safety and efficacy of inhaled fluticasone propionate in children aged 1 to 3 years with recurrent wheezing. *Pediatrics.* 2004;113:e87–e94.
13. Reginster JY, Dethor M, Pirenne H, Dewe W, Albert A. Reproducibility and diagnostic sensitivity of ultrasonometry of the phalanges to assess osteoporosis. *Int J Gynaecol Obstet.* 1998; 63:21–28.
14. Baraldi E, de Jongste JC. Measurement of exhaled nitric oxide in children, 2001. *Eur Respir J.* 2002;20:223–237.
15. Soderstrom L, Kober A, Ahlstedt S, et al. A further evaluation of the clinical use of specific IgE antibody testing in allergic diseases. *Allergy.* 2003;58:921–928.
16. Turner DJ, Stick SM, Lesouef KL, Sly PD, Lesouef PN. A new technique to generate and assess forced expiration from raised lung volume in infants. *Am J Respir Crit Care Med.* 1995;151: 1441–1450.
17. Bisgaard H, Klug B. Lung function measurement in awake young children. *Eur Respir J.* 1995;8:2067–2075.
18. Nielsen KG, Bisgaard H. Discriminative capacity of bronchodilator response measured with three different lung function techniques in asthmatic and healthy children aged 2 to 5 years. *Am J Respir Crit Care Med.* 2001;164:554–559.
19. Nielsen KG, Bisgaard H. Lung function response to cold air challenge in asthmatic and healthy children of 2–5 years of age. *Am J Respir Crit Care Med.* 2000;161:1805–1809.
20. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol.* 1980;92:44–47.
21. Kunz B, Oranje AP, Labreze L, Stalder JF, Ring J, Taieb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology.* 1997;195:10–19.
22. Braun-Fahrlander C, Wuthrich B, Gassner M, et al. Validation of a rhinitis symptom questionnaire (ISAAC core questions) in a population of Swiss school children visiting the school health services: SCARPOL-team: Swiss Study on Childhood Allergy and Respiratory Symptom with respect to Air Pollution and Climate International Study of Asthma and Allergies in Childhood. *Pediatr Allergy Immunol.* 1997;8:75–82.
23. Hilberg O. Objective measurement of nasal airway dimensions using acoustic rhinometry: methodological and clinical aspects. *Allergy.* 2002;57(Suppl):5–39.
24. Sub-Committee on Skin Tests of the European Academy of Allergology and Clinical Immunology. Skin tests used in type I allergy testing: position paper. *Allergy.* 1989;44(Suppl):1–59.
25. Johnston SL, Sanderson G, Pattemore PK, et al. Use of polymerase chain reaction for diagnosis of picornavirus infection in subjects with and without respiratory symptoms. *J Clin Microbiol.* 1993;31:111–117.
26. Al Delaimy WK, Crane J, Woodward A. Is the hair nicotine level a more accurate biomarker of environmental tobacco smoke exposure than urine cotinine? *J Epidemiol Community Health.* 2002;56:66–71.
27. Sorensen M, Autrup H, Hertel O, Wallin H, Knudsen LE, Loft S. Personal exposure to PM_{2.5} and biomarkers of DNA damage. *Cancer Epidemiol Biomarkers Prev.* 2003;12:191–196.
28. Palmes ED, Burton RM Jr, Ravishanker K, Solomon JJ. A simple mathematical model for diffusional sampler operation. *Am Ind Hyg Assoc J.* 1986;47:418–420.
29. Druzik CM, Grosjean D, Neste AV, Parmar SS. Sampling of atmospheric carbonyls with small DNPH-coated C-18 cartridges and liquid chromatography analysis with diode array detection. *Int J Environ Anal Chem.* 1990;38:495–512.
30. Brunekreef B, Smit J, de Jongste J, et al. The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study: design and first results. *Pediatr Allergy Immunol.* 2002; 13(Suppl):55–60.
31. Nickel R, Niggemann B, Gruber C, Kulig M, Wahn U, Lau S. How should a birth cohort study be organised? Experience from the German MAS cohort study. *Paediatr Respir Rev.* 2002;3: 169–176.
32. Williams HC, Burney PG, Strachan D, Hay RJ. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. II: Observer variation of clinical diagnosis and signs of atopic dermatitis. *Br J Dermatol.* 1994;131:397–405.
33. Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by "wheeze"? *Arch Dis Child.* 2000;82:327–332.
34. Cane RS, McKenzie SA. Parents' interpretations of children's respiratory symptoms on video. *Arch Dis Child.* 2001;84:31–34.
35. Committee on Bioethics, American Academy of Pediatrics. Informed consent, parental permission, and assent in pediatric practice. *Pediatrics.* 1995;95:314–317.
36. Smyth RL, Weindling AM. Research in children: ethical and scientific aspects. *Lancet.* 1999;354(Suppl):SII21–SII24.
37. Mielck A, Reitmeir P, Wjst M. Severity of childhood asthma by socioeconomic status. *Int J Epidemiol.* 1996;25:388–393.
38. Bisgaard H, Dalgaard P, Nyboe J. Risk factors for wheezing during infancy: a study of 5,953 infants. *Acta Paediatr Scand.* 1987;76:719–726.
39. Williams HC, Strachan DP, Hay RJ. Childhood eczema: disease

- of the advantaged? *BMJ*. 1994;308:1132–1135.
40. Melnik B, Plewig G. Are disturbances of omega-6-fatty acid metabolism involved in the pathogenesis of atopic dermatitis? *Acta Derm Venereol Suppl (Stockh)*. 1992;176:77–85.
41. Villa MP, Bernardi F, Burnaccini M, et al. Bronchial reactivity and sex hormone: study in a Turner's population. *Pediatr Pulmonol*. 1990;9:199–205.
42. ten Tusscher GW, de Weerd J, Roos CM, et al. Decreased lung function associated with perinatal exposure to Dutch background levels of dioxins. *Acta Paediatr*. 2001;90:1292–1298.
43. Karmaus W, Kuehr J, Kruse H. Infections and atopic disorders in childhood and organochlorine exposure. *Arch Environ Health*. 2001;56:485–492.
44. Strachan DP. Hay fever, hygiene, and household size. *BMJ*. 1989;299:1259–1260.
45. von Mutius E, Martinez FD, Fritzsche C, Nicolai T, Reitmeir P, Thiemann HH. Skin test reactivity and number of siblings. *BMJ*. 1994;308:692–695.
46. Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis." *Thorax*. 2000;55(Suppl):S2–S10.
47. Sepp E, Julge K, Vasar M, Naaber P, Bjorksten B, Mikelsaar M. Intestinal microflora of Estonian and Swedish infants. *Acta Paediatr*. 1997;86:956–961.
48. Johnston SL, Pattemore PK, Sanderson G, et al. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ*. 1995;310:1225–1229.
49. Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet*. 1999;354:541–545.
50. Sigurs N. Epidemiologic and clinical evidence of a respiratory syncytial virus–reactive airway disease link. *Am J Respir Crit Care Med*. 2001;163:S2–S6.
51. Illi S, von Mutius E, Lau S, et al; MAS Group. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *BMJ*. 2001;322:390–395.
52. Leung DY. Atopic dermatitis and the immune system: the role of superantigens and bacteria. *J Am Acad Dermatol*. 2001;45(Suppl):S13–S16.
53. Soyseth V, Kongerud J, Haarr D, Strand O, Bolle R, Boe J. Relation of exposure to airway irritants in infancy to prevalence of bronchial hyper-responsiveness in schoolchildren. *Lancet*. 1995;345:217–220.
54. McConnell R, Berhane K, Gilliland F, et al. Prospective study of air pollution and bronchitic symptoms in children with asthma. *Am J Respir Crit Care Med*. 2003;168:790–797.
55. Chauhan AJ, Inskip HM, Linaker CH, et al. Personal exposure to nitrogen dioxide (NO₂) and the severity of virus-induced asthma in children. *Lancet*. 2003;361:1939–1944.
56. Ownby DR, Johnson CC, Peterson EL. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. *JAMA*. 2002;288:963–972.
57. Taussig LM, Wright AL, Holberg CJ, et al. Tucson Children's Respiratory Study: 1980 to present. *J Allergy Clin Immunol*. 2003;111:661–676.
58. Le Souef P. Prediction of asthma in children at 6 and 12 years of age: Perth infant asthma follow-up study. *Pediatr Allergy Immunol*. 2002;13(Suppl):44–46.
59. Arshad SH, Tariq SM, Matthews S, Hakim E. Sensitization to common allergens and its association with allergic disorders at age 4 years: a whole population birth cohort study. *Pediatrics*. 2001;108:E33.
60. Bergmann RL, Bergmann KE, Lau-Schadensdorf S, et al. Atopic diseases in infancy: the German Multicenter Atopy Study (MAS-90). *Pediatr Allergy Immunol*. 1994;5(Suppl):19–25.
61. Wickman M, Kull I, Pershagen G, Nordvall SL. The BAMSE project: presentation of a prospective longitudinal birth cohort study. *Pediatr Allergy Immunol*. 2002;13(Suppl):11–13.
62. Gold DR, Burge HA, Carey V, Milton DK, Platts-Mills T, Weiss ST. Predictors of repeated wheeze in the first year of life: the relative roles of cockroach, birth weight, acute lower respiratory illness, and maternal smoking. *Am J Respir Crit Care Med*. 1999;160:227–236.
63. Custovic A, Simpson BM, Murray CS, Lowe L, Woodcock A; NAC Manchester Asthma and Allergy Study Group. The National Asthma Campaign Manchester Asthma and Allergy Study. *Pediatr Allergy Immunol*. 2002;13(Suppl):32–37.
64. Lemanske RF Jr. The Childhood Origins of Asthma (COAST) study. *Pediatr Allergy Immunol*. 2002;13(suppl 15):38–43.
65. Backer V, Nepper-Christensen S, Ulrik CS, von Linstow ML, Porsbjerg C. Factors associated with asthma in young Danish adults. *Ann Allergy Asthma Immunol*. 2002;89:148–154.
66. Linneberg A, Nielsen NH, Madsen F, Frolund L, Dirksen A, Jorgensen T. Increasing prevalence of specific IgE to aeroallergens in an adult population: two cross-sectional surveys 8 years apart: the Copenhagen Allergy Study. *J Allergy Clin Immunol*. 2000;106:247–252.

Requests for reprints should be addressed to:
Hans Bisgaard, MD, DMSci
COPSAC Clinical Research Unit L213
Department of Pediatrics
Copenhagen University Hospital; Gentofte
DK-2100 Copenhagen, Denmark
E-mail: Bisgaard@copsac.dk