FAMILIAL AGGREGATION AND RISK FACTORS FOR ASTHMA AND HAY FEVER AMONG FINNISH ADOLESCENT TWINS — A TWIN FAMILY STUDY

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Academic dissertation

To be publicly discussed, by the permission of the Medical Faculty of the University of Helsinki, in Auditorium 2 of Meilahti Hospital, Haartmaninkatu 4, Helsinki, on January 14th 2000, at 12 noon.

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To all families
that have experienced
the worry and the
overwhelming joy
of multiple birth

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ABBREVIATIONS

χ^2	chi-square
CI	confidence interval
DZ	dizygotic
ECP	eosinophil cationic protein
IgE	immunoglobulin E
IL-4	interleukin 4
MHC	major histocompatibility complex
MZ	monozygotic
NO_2	nitrogen dioxide
OR	odds ratio
OS	opposite sex
PEF	peak expiratory flow
RSV	respiratory syncytial virus
SO_2	sulfur dioxide
SS	same-sexed
Th1	T-helper 1 cell
Th2	T-helper 2 cell

LIST OF ORIGINAL COMMUNICATIONS

I Laitinen T, Räsänen M, Kaprio J, Koskenvuo M, Laitinen LA.
Importance of genetic factors in adolescent asthma - a population-based twin-family study.
Am J Respir Crit Care Med 1998;157:1073-8.

II Räsänen M, Laitinen T, Kaprio J, Koskenvuo M, Laitinen LA.
Hay fever - a Finnish nationwide study of adolescent twins and their parents.
Allergy 1998;53:885-90.

III Räsänen M, Laitinen T, Kaprio J, Koskenvuo M, Laitinen LA.
Hay fever, asthma and number of older siblings - a twin study.
Clin Exp Allergy 1997;27:515-8.

IV Räsänen M, Kaprio J, Laitinen T, Winter T, Koskenvuo M, Laitinen LA.
Perinatal risk factors for asthma in Finnish adolescent twins.
Thorax, in press

V Räsänen M, Kaprio J, Laitinen T, Winter T, Koskenvuo M, Laitinen LA.
Is the risk for hay fever determined before or after birth? - A study among 2550 twin families
Submitted

INTRODUCTION

Asthma is the most common chronic disease among children and among the five most common among adults (Haahtela and Laitinen 1996). In Finland, the yearly costs of asthma in the beginning of the 1990's were estimated to exceed 2.5 billion marks, including medication, hospitalisation, sick leave, loss of production, disability, and other indirect costs (Haahtela et al. 1993). Costs for medical treatment of asthma have risen during the 1980's, and were 280 million marks in 1994. Asthma costs are likely to rise, due to the rising incidence of asthma and life expectancy, if the goals for the prevention, treatment, and rehabilitation in the Finnish asthma program are not fulfilled (Haahtela and Laitinen 1996). Compared to other major national health problems the epidemiology and clinical features of asthma have been studied relatively little in Finland (Haahtela and Laitinen 1996).

Allergic rhinitis is even more common among children in Finland than asthma, although not exceeding the occurrence of allergic eczema (Varjonen et al. 1992, Remes et al. 1998). Allergic rhinitis is not regarded as large a health problem as asthma because it is practically never life-threatening and far less often requires hospitalisation, but due to its high prevalence, medical costs, loss of work and of school days, and of quality of life, allergic rhinitis causes significant expense. In Finland as in other western countries, the incidence of allergic rhinitis, as for other allergic diseases, has also risen during the past three decades (Rimpelä et al. 1995, Reijula et al. 1996, Butland et al. 1997b). The causes for this increase are thought to be environmental, but they remain largely unknown.

Twins offer a unique opportunity to study the roles of genes and environment in the development of a disease. In Finland, in addition to a well-established population-based twin cohort study, this opportunity is strengthened by a culturally and genetically homogenous population and almost uniformly co-operative twin families. Furthermore, the FinnTwin16 study offered an opportunity to explore the epidemiology of asthma and hay fever in a representative nation-wide sample of adolescents.

REVIEW OF THE LITERATURE

DEFINITIONS

Asthma

Definitions of asthma have evolved along with the improved understanding of the pathophysiology of asthma, but still at present no single clear-cut definition for asthma exists. The International Consensus Report on the Diagnosis and Treatment of Asthma (1992) defined asthma as follows: 'a chronic inflammatory disorder of the airway in which many cells play a role, including mast cells and eosinophils. In susceptible individuals this inflammation causes symptoms which are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment, and causes an associated increase in airway responsiveness to a variety of stimuli' (Anonymous 1992). This definition cannot, however, be used directly for either epidemiological or clinical purposes. For clinical and research purposes, asthma is often regarded through its components or a combination of these: bronchial hyperreactivity, airway narrowing measured with PEF or forced expiratory volume in one second (FEV1), atopy measured by total or specific serum IgE, or skin prick test, and markers of inflammation (serum or sputum ECP or eosinophils). However, no single feature or group of features is common to all asthmatics (Howell 1995). In epidemiological research, asthma is often defined either through questions relating to the diagnosis of asthma or to asthma symptoms which are preferred over bronchial hyperreactivity testing, due to their greater validity (Pekkanen and Pearce 1999). Asthma may go undiagnosed if subjects, or in the case of children or adolescents, their guardians, do not perceive symptoms as severe enough, or for other reasons do not consult a doctor (Siersted et al. 1998). And for doctors, diagnosis of asthma is difficult due to its characteristic variability in clinical expression both between subjects and within one subject during a lifespan or during even shorter periods.

Hay fever

Allergic rhinitis is an IgE-mediated reaction leading to mucosal inflammation characterised by sneezing, itching, watery nasal discharge, and nasal blockage (van Cauwenberge and Ingelis 1995). Its clinical diagnosis is made on the basis of symptoms and is confirmed with skin prick test (van Cauwenberge and Ingelis 1995). When symptoms of allergic rhinitis are present for only part of a year,

usually during spring and summer months, it is called seasonal. Strictly defined, hay fever is seasonal allergic rhinitis triggered by grass pollen (Sibbald and Rink 1991), but, in practice, seasonal rhinitis triggered by any air-borne pollen (in Finland during April-August) is called hay fever (Charpin et al. 1996). Like asthma, hay fever is often defined for epidemiological purposes through questions relating to its diagnosis or symptoms. Hay fever prevalence is also liable to even short-term changes due to variability in pollen amounts and to some extent due to a subject's behaviour (Ross and Fleming 1994, Remes et al. 1998).

Atopy

Atopy is a person's tendency to form specific IgE antibodies directed at common environmental antigens (Brostoff and Hall 1993). Allergic rhinitis, asthma, and allergic eczema are regarded as atopic diseases (Brostoff and Hall 1993).

PATHOPHYSIOLOGY

Environmental stimuli and genetic susceptibility to atopic sensitisation are thought to interact in the initiation of atopic inflammation, which is characterised by T-cells of an enhanced Th-2 type and a reduced Th-1 cytokine profile (Holgate 1998). This inflammation in the airway epithelium, engaging epithelial cells and submucosal structures as well as migrating cells, gives rise to symptoms and in the case of asthma to bronchial hyperreactivity and airway limitation (Holgate 1998). In asthma, airway limitation measured with pulmonary function tests is typically reversible and periodical and as such is principally due to airway smooth muscle contraction. Morphologically, inflammation leads to damage of the airway epithelium which can already be observed in newly detected asthma (Laitinen et al. 1993). If prolonged, inflammation leads to airway remodelling and persistent airway limitation (Holgate 1998). The mucosal structure and inflammation are similar in the bronchi and nose (Vignola et al. 1998).

NATURAL HISTORY IN CHILDHOOD

The incidence of asthma is highest during the first five years of life, with a gradual decrease until adolescence, with another peak in incidence in adulthood

(Broder et al. 1974, Anderson et al. 1992). In childhood, boys are more often affected but the gender ratio is reversed in adolescence with more incident cases among women in adulthood (Anderson et al. 1992). Most children with wheezing during the first years of life recover, especially those with no atopy or family history of asthma (Martinez et al. 1995). These transient early wheezers show a lower level of lung function, possibly due to congenitally smaller airways (Martinez et al. 1995). Those with persistent respiratory symptoms are often atopic and show bronchial hyperreactivity (Stein et al. 1997). Additionally, those developing asthma later in childhood are more likely to have persistent asthma even until adulthood (Kokkonen and Linna 1993, Oswald et al. 1994).

In childhood, next to infectious rhinitis, seasonal allergic rhinitis is the most common form of rhinitis (Togias 1993). Its incidence in boys rises until adolescence with a clear decline in young adulthood, whereas in girls, incidence is highest in adolescence through young adulthood (Broder et al. 1974, Pedersen and Weeke 1981). Remission of allergic rhinitis before adulthood is not common, but change in the spectrum and severity of symptoms may occur (Linna et al. 1992).

The most recent population surveys in Finland have reported the prevalence of doctor-diagnosed asthma among schoolchildren and adolescents to be 2.5% to 5.7% and that of doctor-diagnosed or self-reported hay fever 14% to 27% (Varjonen et al. 1992, Rimpelä et al. 1995, Timonen et al. 1995, Remes et al. 1996, Pekkanen et al. 1997, Remes et al. 1998). These prevalences are higher than in studies performed in the 1970's and 1980's (1.0%-3.0% and 5.0%-14%) (Malmberg 1979, Haahtela et al. 1980, Pöysä et al. 1991, Rimpelä et al. 1995) and even higher than in earlier studies (0.6%-0.7% and 0.4%) (Eriksson-Lihr 1955, Peltonen et al. 1955).

Recent international large-scale studies of the prevalence of symptoms of atopic diseases, applying similar methods in several countries, have shown large variation between countries (Anonymous 1996, Beasley et al. 1998). In Finland, the prevalence of asthma and hay fever are relatively high compared to that in many central, and particularly, eastern European countries, but lower than in the UK or Australia; whereas the prevalence of atopic eczema in Finnish children is among the highest (Beasley et al. 1998).

An increased prevalence of asthma, hay fever, and atopic eczema in the developed world has been widely reported (Gergen et al. 1988, Burr et al. 1989, Peat et al. 1994, Åberg et al. 1995, Butland et al. 1997b). In Finland, a similar increase has been shown also in studies applying similar methods at different

times (Haahtela et al. 1990, Rimpelä et al. 1995, Reijula et al. 1996, Huovinen et al. 1999). The increase appears too steep to be explained by improved diagnostics and public awareness (Haahtela et al. 1990). Although no increase was found in a meta-analysis (Magnus and Jaakkola 1997), that the increase is being real is supported by studies applying objective measurements of asthma (Burr et al. 1989, Peat et al. 1994, Dubois et al. 1998). Because the increase has taken place during only a few decades, changes in the gene pool are unlikely; more likely causes for the increase in developed countries are changes in environment and behaviour. This was supported by the increase in prevalence of hay fever and atopic sensitisation observed during a relatively short period of time in the former East Germany following reunification and westernisation of living conditions (von Mutius et al. 1998).

GENETIC EPIDEMIOLOGY

Disease aggregation in families does not necessarily imply genetic transmission. The patterns and temporal aspects of familial clustering can offer clues to whether the disease is of genetic, infectious, or environmental origin (Khoury et al. 1993). After evidence for familial aggregation of a disease exists, environmental, cultural, and genetic factors contributing to the aggregation can be distinguished. Finally, specific genetic mechanisms can be analysed (Khoury et al. 1993). Different study approaches and designs contribute to understanding of the genetic architecture of a disease.

Family studies

Family studies offer evidence for familial aggregation of a trait, allow for distinction between environmental and genetic factors contributing to this clustering, and are useful in determining the mode of inheritance (Khoury et al. 1993). Observations on familial aggregation of asthma and allergic diseases are not new (Salter 1860, Cooke and Vander Veer Jr 1916). Around 50% of persons with an atopic disease have a positive family history (Dold et al. 1992, Varjonen et al. 1992). Often-used measures of increased risk are, depending on the study design, the rate ratio, odds ratio, and family relative risk (Khoury et al. 1993).

Various studies are quite consistent on the recurrence risk for asthma: in a person with one affected first-degree relative, the risk is two- to three-fold that for persons with a negative family history of asthma (Luoma et al. 1983, Dold et al.

1992, Burrows et al. 1995, Anonymous 1997, Jenkins et al. 1997, Litonjua et al. 1998), with the risk linked to an affected sibling slightly but not significantly higher than that linked to a parent (Diepgen and Blettner 1996, Jenkins et al. 1997). For other atopic diseases, the risk with an affected family member has been similar to that of asthma (Fergusson et al. 1983, Luoma et al. 1983, Dold et al. 1992, Diepgen and Blettner 1996). If both parents have asthma, the risk is four- to six-fold (Dold et al. 1992, Burrows et al. 1995, Litonjua et al. 1998). A Finnish study on three generations showed a 25-fold risk for asthma in the offspring when there was asthma in both previous generations (Luoma and Koivikko 1982).

Some studies have found a higher risk for atopic diseases through the maternal line especially in early childhood (Cookson et al. 1992, Ruiz et al. 1992, Litonjua et al. 1998), while larger population-based studies have found no significant differences in risk by parental gender (Dold et al. 1992, Burrows et al. 1995, Anonymous 1997, Jenkins et al. 1997). Several studies have shown that a specific type of allergic disease in the parents increases the risk for that disease in the offspring, suggesting that, in addition to general liability to atopic diseases, liability to a specific type of expression is inherited (Luoma and Koivikko 1982, Fergusson et al. 1983, Dold et al. 1992, Litonjua et al. 1998). The same specific liability appears to apply also to intrinsic and extrinsic asthma which aggregates in families (Pirson et al. 1991, Anonymous 1997).

Components of asthma also aggregate in families, with different modes of inheritance for these components suggested (Lebowitz et al. 1984, Townley et al. 1986, Longo et al. 1987). However, recent studies have also suggested that the inheritance of asthma may not be mediated through inheritance of these intermediate phenotypes (Burrows et al. 1995, von Mutius and Nicolai 1996, Givelber et al. 1998, Holberg et al. 1998). Molecular genetic studies on asthma and atopy lend support to the concept of asthma's genetic heterogeneity (Barnes and Marsh 1998).

Adoption studies

Since adoptees share no genes with their adoptive parents, any excess similarity between them can be attributed to shared family environment (Plomin et al. 1994). Very few adoption studies exist concerning atopic diseases. Among 367 families with adoptive children, asthma or allergic rhinitis in the mother but not in the father increased the risk for corresponding disease in the adoptees,

suggesting a component of shared family environment in development of these diseases (Smithe et al. 1998).

Twin studies

Classical twin method

The first step towards discovering the molecular genetic architecture of a trait is to show that the trait is genetically influenced (Martin et al. 1997). The classical twin study design estimates the contribution of genes and environment by comparing the similarity of MZ twins to that of DZ twins (Falconer and MacKay 1995)ADDIN. Differences within a MZ pair are attributable to environment because MZ twins are regarded as genetically identical, whereas differences within a DZ pair are due both to environment and to genes, which they share on average 50%, as do siblings in general. Higher concordance, i.e., similarity in the studied trait, within MZ pairs than within DZ pairs indicates genetic influence on the development of the trait. Heritability estimates, i.e., the proportion of genetic variance to total variance, can be derived by using either concordances or twin correlations (Parisi 1995). One central assumption underlying the design is that environments within MZ pairs are similar to those within DZ pairs (Falconer and MacKay 1995 239), and this has been shown to be generally true for postnatal environments (Kendler et al. 1993). However, several factors may lead to differences in intrauterine environments within and between DZ and MZ pairs (Martin et al. 1997).

Structural equation modelling

The structural equation models developed during the 70's and 80's have advantages over the classical twin approach: they can be applied to quantitative measurements and in family and adoptee settings, can estimate different components of genetic variance (additive and non-additive), or can distinguish between genetic and shared environmental effects. Furthermore, different models can be compared by goodness-of-fit statistics (Neale and Cardon 1992).

The basic model is one in which the individual's deviation from the population mean is assumed to result from both genetic and environmental effects (Neale and Cardon 1992). Genetic effects may be due to additive genetic effects (i.e., the allele-specific average effects at a locus, summed over all relevant loci) or non-additive effects (due to interactions within a locus, known as dominance, or

between loci, known as epistasis) (Neale and Cardon 1992). Environmental effects can be further divided into shared and non-shared effects. Shared environmental effects refer to those that are shared by family members living in the same household, such as parental socio-economic status, religious affiliation, indoor-air quality and so on, while the non-shared are unique to each individual, and thus not shared by family members (Neale and Cardon 1992). In terms of variability, the corresponding phenotypic variance is assumed to result from genetic and environmental variances.

Co-twin control study

Because MZ twins are genetically identical, differences in the expression of a trait between the twins are due to environment. In a study design using the co-twin as the control for the other twin allows controlling for genetic causes for the trait studied (Duffy 2000). Co-twin control study may be experimental or observational for an exposure or case-control (twins discordant for the outcome of interest) (Duffy 2000). In the latter, by identifying twin pairs discordant for a trait and comparing difference in their exposures, allows tracing of etiological factors for a trait (Kaprio 1991). Incorporating discordant DZ pairs in to the study allows for additional inference about genetic and environmental contributions to the trait-exposure association (Duffy 2000).

Twin studies on asthma

Large population-based twin studies on asthma can be divided into two generations according to year of birth of the twins either in the first or second half of the twentieth century (Table 1). Most of the studies are from Nordic countries in which representative population-based twin registries have been established (Kaprio et al. 1990). In Australia, the twin registry consists of recruited volunteers but can be regarded as representative in respect to asthma because neither recruitment nor data collection was limited to asthma or allergies (Duffy et al. 1990). In order to allow comparison, heritability estimates for the first generation studies in Table 1 are reported calculated with structural equation modelling (Duffy 1992), which has been used in all the second generation studies.

The over eight-fold differences in asthma occurrence between the studies are probably due to geographical variation in asthma prevalence, differences in asthma definition, and in data collection (Anonymous 1996). Nonetheless, the

second generation studies end with very similar, high heritability estimates (62%-79%). Heritabilities in the older studies are somewhat lower, which may be due to the older study subjects. Common to all these studies is the negligible proportion of variance due to shared environment; a unique environment accounting for 21% to 56% of variance in liability to asthma.

Among older Finnish twins, the heritability (h^2) calculated from phenotypic correlations (r) for zygosity groups [$h^2=2(rMZ-rDZ)$] showed a remarkable gender difference, being zero in men and 68% in women (Nieminen et al. 1991). This was probably due to the small number of asthma-concordant men. However, when Duffy (1990) applied equation modelling to the Finnish data, no heterogeneity due to gender could be shown, whereas among Australian twins, non-additive genetic effects were suggested in men and additive in women. In later studies, gender differences have either not been found or have not been studied, apart from allowing for different thresholds in the models.

Twin studies on components of asthma

Smaller-scale twin studies have shown higher concordance in MZ than in DZ pairs for serum total IgE (Bazaral et al. 1974, Sistonen et al. 1980, Hopp et al. 1984, Hanson et al. 1991), bronchial hyperreactivity (König and Godfrey 1973, Townley et al. 1976, Hopp et al. 1984), pulmonary function (Redline et al. 1987), skin prick test score (Hopp et al. 1984), and IgE-mediated basophil releasability (Marone et al. 1986), but not for allergen-specific IgE or skin prick test (Hopp et al. 1984, Hanson et al. 1991). In spite of the relatively small numbers of twins studied and non-random recruitment of the subjects in these studies, that their results are parallel indicates genetic control of components of asthma. Heritability estimates for these traits have ranged between 56% and 72%, similar to those for asthma.

When MZ pairs of the older Finnish twin cohort discordant for asthma were compared for occupational exposure, smoking and exposure to organic solvents were found only among asthmatics, suggesting the role of these irritants in the development of asthma (Antti-Poika et al. 1992). In a more recent study, Duffy et al. (1998) studied 124 Australian twin pairs discordant for wheeze for markers of atopic sensitisation. The affected co-twins had significantly higher total IgE and had larger skin prick test wheals than did their unaffected co-twins for cat and house-dust mite, allergens associated with asthma in Australia (Sears et al. 1993). Intrapair differences for wheal size were not found for pollen. The authors suggested this as evidence of sensitisation to indoor allergens as being an

Table 1. Twin studies estimating the heritability of asthma.

Country	Study year	Population source	Twin type	Method	Definition of asthma	Number of pairs	Age (y)	Prevalence Male Female	Heritability Male Female	Study
First generation										
Sweden	1967	Population registry	SS	Q [a)]	Ever asthma	6,996	42-81	3.5% 4.0%	63% [b)]	Edfors-Lubs 1971
Australia	1980-2	Recruited registry	All	Q	Ever asthma or wheezing	3,808	18-88	13.8% 12.9%	74% 58%	Duffy et al. 1990, Hopper et al. 1990
Finland	1975	Population registry	SS	RL [c)]	Dg by doctor [d)]	13,888	18+	1.7% 2.1%	44% [b)]	Nieminen et al. 1991
Second generation										
Norway	1992	Population registry	All	Q	Ever asthma	2,570	18-25	6.0% 5.4%	75%	Harris et al. 1997
Sweden	1994	Population registry	All	Q	Ever or current asthma	1,339	7-9	18% 10%	76% 62%	Lichtenstein and Svartengren 1997
Finland	1991-4	Population registry	All	Q	Dg by doctor	1,713	16	3.9%	79%	Present study (I)
Denmark	1994	Population registry	All	Q	Ever asthma	12,352	12-41	6.2%	73%	Skadhauge et al. 1999

a) Q = questionnaire
b) Heritability estimates as calculated by Duffy (Duffy 1992)
c) RL = record linkage
d) Dg = diagnosed

Table 2. Twin studies estimating the heritability of hay fever.

Country	Study year	Population source	Twin type	Method	Definition of hay fever	Number of pairs	Age (y)	Prevalence Male Female	Heritability Male Female	Study
Sweden	1967	Population registry	SS	Q [a)]	Ever hay fever	6,996	42-81	15.5% 14.2%		Edfors-Lubs 1971
Australia	1980-2	Recruited registry	All	Q	Ever hay fever	3,808	18-88	29.7% 33.4%	60%	Duffy et al. 1990, Hopper et al. 1990
Sweden	1994	Population registry	All	Q	Ever or current hay fever	1,339	7-9	12% 8%	33% 70%	Lichtenstein and Svartengren 1997
Finland	1991-4	Population registry	All	Q	Dg by doctor [b)]	1,765	16	12.0%	82%	Present study (II)

a) Q = questionnaire
b) Dg = diagnosed

intermediate step in the development of asthma in atopic persons (Duffy et al. 1998). When they studied further the concordance for allergen-specific IgE responses to different rye-grass allergens, they found no evidence for genetic control (Sluyter et al. 1998).

Twin studies on hay fever

Only a few twin studies have explored hay fever, but those that have done so, have studied both asthma and hay fever simultaneously (Edfors-Lubs 1971, Duffy et al. 1990, Hopper et al. 1990, Hanson et al. 1991, Lichtenstein and Svartengren 1997). This approach allows estimation of genetic correlation between liabilities to these diseases. MZ twins have shown higher concordances for hay fever than DZ twins, with heritability estimates ranging from 33% to 82% (Table 2). Among adult Australian twins, a model composed of additive genetic and unique environmental effects fitted the data best, with no indication of gender differences, leading to a heritability estimate of 60% (Duffy et al. 1990). Among Swedish twins age 7 to 9, additive genetic effects accounted for 33% of the variation in liability to hay fever in boys and 70% in girls, with shared environmental effects accounting for 48% and 14% of the variation (Lichtenstein and Svartengren 1997). At such a young age, the study subjects may not have reached the peak of hay fever incidence, and they share an environment more than adults do; facts which may have led to differences within and between the studies.

Use of log-linear modelling on the Australian data revealed common genetic background for both asthma and hay fever (Hopper et al. 1990). The extent to which the same genes contribute to the phenotypic correlation observed between two traits, i.e., the genetic correlation between the diseases, was estimated to 0.65 for women and 0.52 for men, and environmental correlations to 0.33 and 0.53 (Duffy et al. 1990). Among young Swedish twins, the genetic correlation between asthma and hay fever was higher (0.90) than cross-correlations between asthma and other atopic manifestations (eczema and urticaria) (Lichtenstein and Svartengren 1997).

Molecular approaches

The ultimate goals for identifying the genes for asthma and atopy are 1) to define new pathophysiological mechanisms for the development of the disease(s) 2) to find new targets for drug development, and 3) to be able to define a risk population that may benefit from intervention measures (Hall 1999). In contrast

to monogenic diseases inherited under Mendelian laws, atopic diseases are regarded as complex diseases. Such diseases 1) exhibit locus heterogeneity, i.e., different genes or different groups of interacting genes cause similar phenotypes, and 2) are multifactorial, i.e., expression of the disease is determined – in addition to interactions between several genes – also by multiple environmental factors (Barnes and Marsh 1998). Due to this complexity, the genetics of asthma and related traits, such as IgE, bronchial hyperreactivity, and atopy have been difficult to elucidate (Hall 1999).

Two different approaches to finding asthma genes have been undertaken: genome screens, in which the whole genome is searched with a number of genetic markers for linkage. These studies have revealed several chromosomal regions of potential interest in chromosomes 5q31, 6p21, 11, 12q, and 13 (Barnes and Marsh 1998). In the candidate-gene approach, biologically interesting genes are studied, including the β-2-adrenergicreceptor, IL-4 cytokine cluster, MHC, high and low affinity IgE receptor, IL-4 receptor, and CD 14 genes (Holgate 1997). Thus far, results have not identified conclusively any allelic variant which would increase risk for asthma in several study populations: among Finns, no linkage between serum IgE level or asthma and markers of IL-4 cytokine cluster were found, indicating genetic heterogeneity between populations (Laitinen et al. 1997).

ADDINLarge efforts towards finding genes for complex diseases such as asthma and atopy will eventually lead to understanding of their molecular basis. Before this goal is achieved, the results of linkage studies need to be repeated in different populations, genes and mutations identified, and the function of these genes in disease established (Barnes and Marsh 1998).ADDIN

ENVIRONMENTAL RISK FACTORS

Environmental risk factors are characteristics of a subject or his/her environment or behaviour that are associated with the occurrence of the disease. Risk factors may be causal or non-causal, and evidence for causality comes from a variety of sources, of which epidemiological studies form one part (Rothman 1986).

Perinatal risk factors

Elevated blood pressure, impaired glucose tolerance, and coronary heart diseases have been linked to suboptimal development during fetal life (Barker 1995). The

Table 3. Studies exploring perinatal risk factors for respiratory health published during the 1990's.

Outcome	Country	Population	Data collection method [a)]	No. of subjects	Age at study (y)	Factors increasing risk	No significant associations observed	Study
Asthma dg, current	USA	Population sample	Maternal I	5,672	0,5 - 11	Low birth weight Young maternal age Low income	Prematurity	ADDIN Schwartz et al. 1990
Asthma dg	Israel	Military recruits	I, PE, RL	20,312	17	Low birth weight Second born High paternal education	BMI at study Residence area	ADDIN Seidman et al. 1991
Asthma Atopy	Germany	Population sample	Parental Q, PFT, BHR, SPT	5,030	9-11	—	Prematurity,	ADDIN von Mutius et al. 1993
Asthma	Germany	School children	Parental Q, SPT	1,812	Primary -school age	Male gender Prematurity Parental asthma Young maternal age	Parental education Maternal smoking during first year	ADDIN Frischer et al. 1993
Asthma	New Zealand	Birth cohort	Q	1,037	18	Birth weight 3000-3500 g	—	Sears et al. 1996
Asthma dg	USA	Case-control	BR, MR	131+131	4-9	Low birth weight &length Low gestational age Maternal smoking Maternal asthma Ventilatory support	—	ADDIN Oliveti et al. 1996
Asthma dg	New Zealand	Birth cohort	Parental I, MR	1,265	16 .	Head circumference > 37 cm Parental asthma Parental allergic rhinitis	Birth weight Birth length Gestation Ratio measures	ADDIN Fergusson et al. 1997

Asthma history by doctor	Sweden	3 national cohorts of conscripts	RL	149,398	17-20	Low birth weight Young maternal age Singleton gestation Small sibship	Gestational age Apgar score Neonatal respiratory disorder SGA	Bråbäck and Hedberg 1997
Asthma	UK	Birth cohort	MR, Q	6,420	26	Low birth weight Small sibship	Maternal smoking in pregnancy	ADDIN Shaheen et al. 1999
Wheeze (persistent) at 16 y	UK	Birth cohort	I, Q	15,712	16	Low maternal age High social status	Birth weight Gender Length of gestation Maternal smoking No. of older siblings	Lewis et al. 1995
Wheeze incidence	UK	Birth cohort	Parental I	5,801	8-16	Male gender Hay fever	Social class Maternal smoking Maternal age Birth order Gestation (</> 37 w)	ADDIN Strachan et al. 1996a
Respiratory symptoms	UK	National sample	Parental Q, PFT	5,573	5-11	Prematurity	—	Rona et al. 1993
Respiratory symptoms	Norway	Population sample	Q, RL	690	20-24	Low birth weight Low maternal age	—	Svanes et al. 1998
Lung function and COPD mortality	UK	Men with MR in childhood	MR, DR, I, PFT	5,718 + 825	59-70	Low birth weight Childhood respiratory infections	—	Barker et al. 1991
Lung function	Germany	Population sample	Parental Q, PFT, BHR, SPT	5,030	9-11	Mechanical ventilation Prematurity (in girls)	—	ADDIN von Mutius et al. 1993
Lung function	UK	National sample	Parental Q, PFT	5,573	5-11	Birth weight (positive association)	—	Rona et al. 1993

a) Explanations for abbreviations: Interview (I), physical examination (PE), record linkage (RL), questionnaire (Q), pulmonary function tests (PFT), bronchial hyperreactivity (BHR), skin prick test (SPT), birth records (BR), medical records (MR), small for gestational age (SGA), death records (DR).

Table 4. Studies exploring perinatal risk factors for atopic diseases other than asthma published during 1990's.

Outcome	Country	Population	Data collection method [a)]	No. of subjects	Age at study (y)	Factors increasing risk	No significant associations	Study
								ADDIN
Hay fever dg	UK	Birth cohort	BR, parental I & Q, SPT	11,765	11-16	High maternal age Small sibship	Parental education Neonatal infection	Strachan et al. 1996b
								ADDIN
Hay fever prevalence	UK	2 birth cohorts	Parental I	15,567	16	Small sibship High maternal age No maternal smoking during pregnancy High social class	—	Butland et al. 1997b
Hay fever history by doctor	Sweden	3 national birth cohorts of conscripts	RL	149,398	17-20	High gestational age High Apgar score Small sibship High maternal age Singleton birth	—	Bråbäck and Hedberg 1997
Hay fever	UK	Birth cohort	MR, Q	6,420	26	High birth weight Small sibship	—	Shaheen et al. 1999
Eczema	New Zealand	Birth cohort	Parental I, MR	1,265	16	—	Birth weight Birth length Gestation Head circumference Ratio measures	Fergusson et al. 1997
								ADDIN
Eczema prevalence	UK	2 birth cohorts	Parental I	15,567	16	Small sibship High maternal age No maternal smoking during pregnancy High social class	—	Butland et al. 1997b
Eczema dg	Denmark	Birth cohort	BR, MR, parental Q	7,862 & 985	5-8	Small sibship High gestational age Increasing birth weight	Gender Maternal age Mat. smoking in pregn	Olesen et al. 1997
Eczema	UK	Birth cohort	MR, Q	6,420	26	—	Birth weight	Shaheen et al. 1999
Serum IgE (>80 IU/ml)	UK	Men and women with BR	MR, I, IgE	280	50	Head circumference >14 inch Adult height, Gender Current smoking	Birth length Ponderal index Placental weight	Godfrey et al. 1994

a) Explanations for abbreviations: birth records (BR), interview (I), questionnaire (Q), skin prick test (SPT), record linkage (RL), medical records (MR), serum total immunoglobulin E (IgE).

fetal-origin hypothesis based on these findings states that fetal adaptation to limited oxygen and nutrient supply program the postnatal physiology and metabolism of the body adversely (Barker 1995). Nutritional status of the fetus, as reflecting the intra-uterine environment and measured as birth characteristics, has been shown to be associated with reduced lung function in later life (Barker et al. 1991, Rona et al. 1993, Fergusson et al. 1997) (Table 3).

Low birth weight and young maternal age have been associated with asthma in some studies (Seidman et al. 1987, Bråbäck and Hedberg 1997, Shaheen et al. 1999), but lack of any association or even contradictory results have been reported (Lewis et al. 1995, Strachan et al. 1996b, Fergusson et al. 1997). Prematurity, especially pulmonary prematurity requiring mechanical ventilation, is also a risk factor for wheezing illness in childhood (von Mutius et al. 1993). Associations between perinatal factors and other atopic manifestations have shown trends somewhat the opposite of from those for asthma. Large head circumference, high gestational age, and high maternal age have been reported to increase risk for hay fever (Strachan et al. 1996b, Bråbäck and Hedberg 1997), atopic eczema (Olesen et al. 1997), or high serum IgE (Godfrey et al. 1994) (Table 4). A higher prevalence of hay fever among those of higher birth weight has also been reported (Lewis et al. 1995, Fergusson et al. 1997, Shaheen et al. 1999). Population-based studies on perinatal risk factors for atopic manifestations, and their associations with pulmonary function are shown in Tables 3 and 4.

Gender

Gender is regarded here as an environmental factor because in the epidemiological literature it is considered a broad indicator of biological and social differences between the two sexes. Boys are at higher risk for development of asthma, hay fever, and atopic sensitisation until adolescence, when hormonal changes are thought to influence susceptibility to atopic diseases (Weiss 1998). The higher risk for wheezing in early childhood in boys is partly explained by their relatively larger lungs and thinner airways compared to those of girls (Weiss 1998). In adulthood, women are at higher risk for atopic diseases than are men (Reijula et al. 1996).

Sensitisation to allergens

Sensitisation to common aeroallergens and/or personal history of atopic disease is often regarded as the most important risk factor for hay fever and asthma.

However, on the population level, cases attributable to atopy have been estimated to be less than 50% of all asthma cases (Pearce et al. 1999). Asthmatics are more often sensitised to indoor allergens, such as the house dust mite, cat, and cockroach, whereas sensitisation to airborne pollen is associated with hay fever (Sears et al. 1993). Level of exposure in early childhood is associated with level of sensitisation later (Sporik et al. 1990), and cross-sectional prevalence of asthma and bronchial hyperreactivity increase with the level of house dust mite allergen in the bed (Peat et al. 1996). However, all those showing a positive skin prick test or specific IgE to allergens do not develop disease (Haahtela et al. 1980), and antigen levels in different climatic regions are not reflected in asthma prevalence, suggesting that individual susceptibility to disease manifestation is important (Peat et al. 1995).

Family size

In a large prospective questionnaire study among British children followed up until adulthood, the number of older siblings was found to be inversely related to occurrence of hay fever (Strachan 1989). A similar inverse relation between number of siblings and skin test reactivity was observed among German schoolchildren (von Mutius et al. 1994). The working hypothesis based on these findings was that cross-infections from older siblings during early childhood may prevent atopic sensitisation (Strachan 1995). The role of family size and childhood infections in the development of both asthma and other atopic diseases has been widely studied ever since (Table 5). A consistent finding is that large sibship is protective against hay fever and probably against atopic sensitisation independent of social status, whereas findings on other atopic manifestations and asthma are not as consistent. However, the studies that have looked at childhood infections or their surrogates simultaneously have not been able to show their protective effect (Broder et al. 1974, Pekkanen et al. 1999, Ponsonby et al. 1999)

Infections

Although viral respiratory infections are known to trigger asthma symptoms both in children and adults (Nicholson et al. 1993, Johnston et al. 1995), their role in asthma inception is unclear (Johnston 1998). Viral infections may increase airway response to allergens and those with a history of RSV bronchiolitis do have a higher incidence of asthma (Johnston 1998). However, several studies suggest that infections may be protective against atopic sensitisation (Shaheen et al. 1996, Matricardi et al. 1997, Shirakawa et al. 1997, Kramer et al. 1999). The possible immunological basis for this finding would be the deviation of T-cell

reactivity towards pathogens (Th1-type) instead of allergic reactivity (Th2-type) (Johnston 1998).

The differential effect of childhood infections and their corresponding vaccinations on the immune system has been suggested; infections may be protective against atopic diseases whereas corresponding vaccination may enhance their development (Shaheen et al. 1996, Farooqi and Hopkin 1998, Lewis and Britton 1998). However, possible confounding exists, based on birth order (Lewis and Britton 1998). These studies' findings appear to correspond with a lower prevalence of atopy among children attending Steiner schools in Sweden. These children were less often vaccinated than control children were, but differences were also observed in several other life-style factors including diet and antibiotic use (Alm et al. 1999).

The day-care setting provides an opportunity to study the effects of childhood respiratory infections on subsequent atopic diseases. Children attending day-care have more otitis media, lower respiratory tract infections, and wheeze (Backman et al. 1984, Marburg et al. 1997). Finnish studies found no decrease in risk for atopic disease in children attending day care centres (Backman et al. 1984, Pekkanen et al. 1999), whereas among German children of small families those who were attending day-care when under one year of age had a lower risk for asthma, hay fever, and skin prick test reactivity than did those attending day-care later (Kramer et al. 1999).

Diet

Prolonged breastfeeding has been suggested to lower the incidence of atopic diseases, but no consensus on the effect of breast-feeding and maternal allergen avoidance has been reached (Saarinen and Kajosaari 1995, Weiss 1997). High intake of sodium, low intake of magnesium, and vitamin C have all shown an association with lung function impairment and asthma, and a positive association with dietary fish intake and pulmonary function and reduction in bronchial hyperreactivity has been suggested (Weiss 1997). Very recently, a large international study has reported a positive association between *trans* n-3 and n-6 fatty acid intake and prevalence of atopic diseases (Weiland et al. 1999). The role of dietary factors in the inception of atopic diseases remains to be elucidated (Weiss 1997).

Table 5. Studies exploring the effect of family size on atopic manifestations. [a)]

Study	No. of subjects	Age at study (y)	Asthma or wheeze	Hay fever	Eczema	Skin prick test	Specif ic IgE	Total IgE	Covariates and additional results
Peat et al. 1980			No	—	—	—	—	—	—
Strachan 1989	Over 9,000	11 & 23	—	OS & YS	OS	—	—	—	—
von Mutius et al. 1994	6,786	9-11	—	—	—	S	—	—	—
Crane et al. 1994	708	8-13	OS	—	—	—	—	—	—
Sears et al. 1996	868		No	—	—	No	—	—	—
Strachan 1995	12,355	23	—	OS & YS	—	—	—	—	Social class as covariate
Lewis et al. 1996	18,883	16	No	—	—	—	—	—	—
ADDIN									
Strachan et al. 1996b	11,765	11-16	—	OS & YS	—	—	—	—	Infection during first moth not protective
Strachan et al. 1997	1,369	34	—	—	—	OS	—	—	—
Jarvis et al. 1997	1,159	20-44	S [b)]	S & BO	No	—	S [c)]	No	—
Rona et al. 1997	11,924	5-11	3+	—	—	—	—	—	Parental history as covariate
Forastiere et al. 1997	2,226	7-11	—	—	—	4+	—	—	Father's education as covariate
Present study (III)	2,680	16	No	OS	—	—	—	—	—
Bråbäck and Hedberg 1997	149,378	17-18	OS [d)]	OS	—	—	—	—	Maternal age as covariate
Bodner et al. 1998	2,111	10-14	3+ YS	3+OS	3+OS	—	—	—	Common childhood infections not protective
Matricardi et al. 1998	11,371	18-24	—	—	—	—	S & BO	—	Father's education
Mattes et al. 1998	3,165	6-9 [e)]	—	OS [f)]	—	—	—	—	g)
Rona et al. 1999	3 x 9,000	5-11	1+	—	—	—	—	—	Study year as covariate
Schafer et al. 1999	1,235	5-6	—	—	—	S	—	—	—
Svanes et al. 1999	13,932	20-44	—	—	—	—	S	—	h)
ADDIN									
Ponsonby et al. 1999	863		No	S	—	—	—	—	i)
Pekkanen et al. 1999	8,387	13-14	3+	3+	3+	—	—	—	Daycare increases hay fever

a) Different possibilities for association: not studied (—), not observed (No), negative association with number of older siblings (OS), younger siblings (YS), siblings (S), n or more siblings (n+), or birth order (BO).

b) No association with respiratory symptoms

c) Only grass sensitivity

d) Only among those with hay fever

e) Age of probands

f) At least two of either asthma, hay fever, or eczema

g) Education and maternal age as covariates. Interaction with paternal atopy.

h) Only in those with no parental atopy. Brothers protective

i) Upper respiratory tract infection during first month not protective.

Smoking

During the past decades, indisputable evidence has accumulated as to the harmful effects of both passive and active tobacco-smoke exposure on respiratory health. A recent series of systematic reviews has summarised the evidence for the effects of environmental tobacco smoke exposure on different aspects of children's respiratory health (Cook and Strachan 1997c, Cook and Strachan 1997a, Cook and Strachan 1997b, Strachan and Cooke 1997, Strachan and Cook 1998b, Strachan and Cook 1998a). Either or both parents' smoking increases their children's risk for asthma and other symptoms in the lower respiratory tract through their entire childhood, more so during the early years (Cook and Strachan 1997a, Strachan and Cooke 1997). The effect of maternal smoking even during pregnancy on PEF and spirometric indices is also significant, although is not so evident on bronchial hyperreactivity (Cook and Strachan 1997c, Cook and Strachan 1997b). No consistent association has, however, been observed between environmental tobacco-smoke exposure and either hay fever, atopic eczema, serum IgE, or skin prick test reactivity (Strachan and Cook 1998a).

Variation in environmental tobacco smoke exposure between Nordic countries has been reported; the number of households exposing children to environmental tobacco smoke was smallest in Finland (7%), suggesting less of a detriment in Finland to children's lung health from smoking (Lund et al. 1998). Even a relatively short period of active smoking in adolescence or teenage has been shown to increase the risk for asthma and upper and lower respiratory symptoms (Larsson 1995, Burr et al. 1999).

Home environment

In the home, common sources of allergens associated with asthma are house dust mites, domestic animals (cats and dogs), and insects such as cockroaches, as well as fungi. Dampness and moulds, wall-to-wall carpets, synthetic bedding, and poor insulation coupled with poor ventilation, and have been associated with increased respiratory symptoms, asthma severity, and prevalence of allergic diseases (Jaakkola et al. 1993, Strachan and Carey 1995, Åberg et al. 1996, Butland et al. 1997a, Williamson et al. 1997). These associations may be mediated by increased exposure to the house dust mite (Brunekreef 1999, Custovic and Woodcock 1999). The association between various heating fuels or pets and allergic diseases is controversial, but smoking indoors clearly appears to be the most important indoor factor affecting respiratory health in childhood

(Strachan and Carey 1995, von Mutius et al. 1996, Butland et al. 1997a, Garrett et al. 1998, Burr et al. 1999).

Pollution

The main outdoor pollutants are particulates, SO_2, NO_2, and ozone. These are known to aggravate asthma symptoms (Pönkä 1991, Timonen and Pekkanen 1997). However, evidence is lacking for their effect in the inception of asthma (Anderson 1997). Comparative studies of asthma and atopy in Germany showed higher prevalences of these traits in the former West Germany than in the more polluted former East Germany, a fact which does not lend support to the importance of pollution in the development of asthma and allergies (von Mutius et al. 1992, Heinrich et al. 1998). In addition, the trends in the prevalences of atopic diseases and pollutant emissions are not parallel (Anderson 1997). However, exhaust particulates may act as adjuvants, increasing the allergenic capability of common aeroallergens (Takafuji et al. 1987).

Several environmental risk factors for atopic diseases have been suggested. However, no evidence exist that any single environmental factor accounts for the increase in atopic diseases over the past decades, which has been shown especially among younger age-cohorts (Gergen et al. 1988, Reijula et al. 1996). Previous studies have suggested that biological changes towards atopic reactivity may take place in early childhood or even before birth (Strachan 1995). Against this background, maternal smoking, other prenatal influences, and early childhood environment may well be factors of importance in the increased atopic burden.

AIMS OF THE STUDY

The aims of the study were to:

1. estimate genetic and environmental contributions to variability in liability to asthma and hay fever among adolescents.

2. identify environmental risk factors for the development of asthma and hay fever among Finnish adolescents.

3. study perinatal factors as risk factors for asthma and hay fever in a twin population with its distribution of perinatal characteristics different from that among singletons

4. study how parental asthma and hay fever status modify the variability in liability to asthma and hay fever, and to study how parental asthma and hay fever status modify the effect of risk factors for asthma and hay fever among adolescents.

METHODS

STUDY POPULATION

Finnish Twin Cohort study

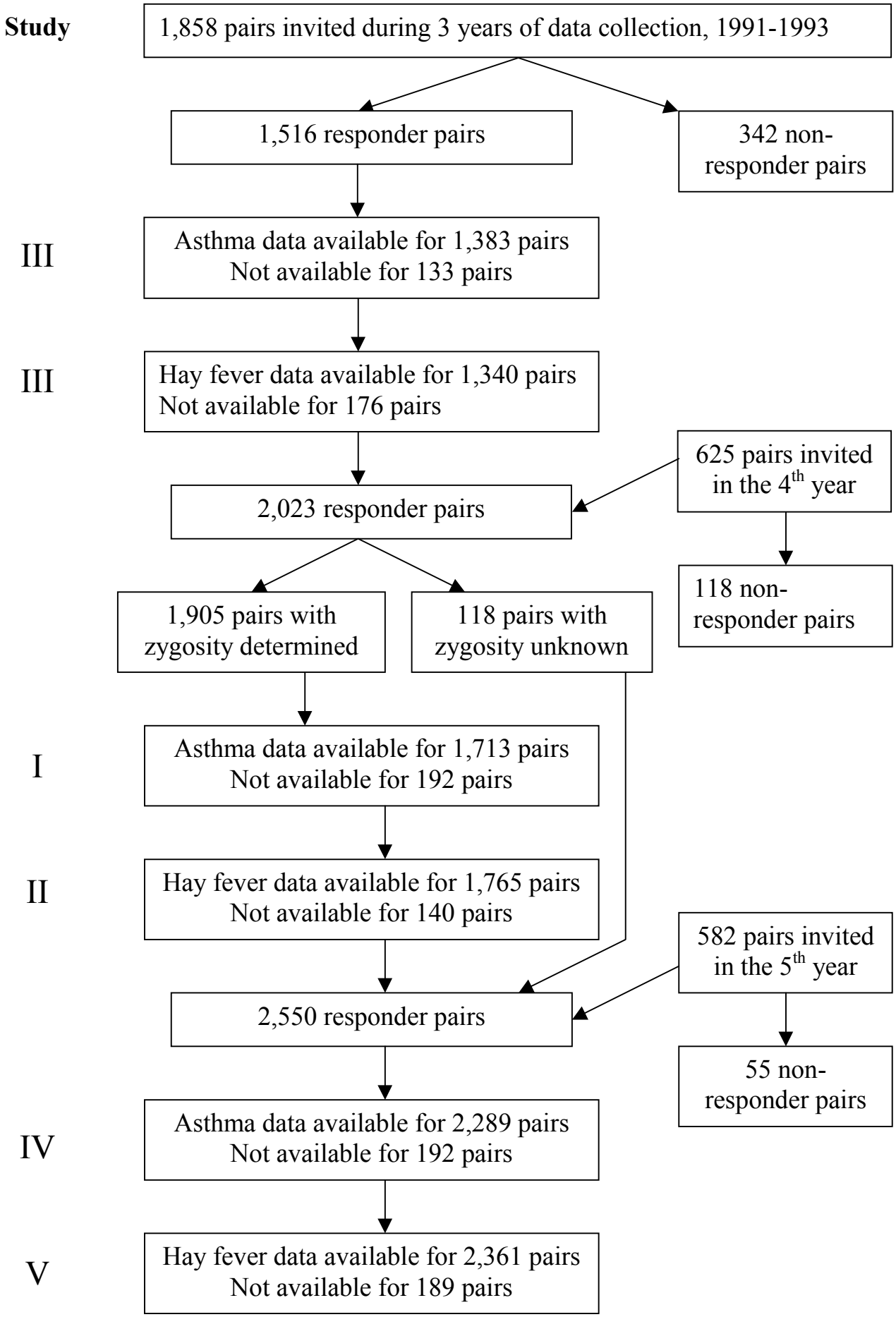
The Finnish Twin Cohort Study is a project for the study of genetic and environmental determinants of chronic diseases and risk factors (Kaprio et al. 1990). The older Finnish twin cohort (17,000 pairs) consists of all same-sexed pairs born before 1958 with both twins alive in 1967 (Kaprio et al. 1990). The younger Finnish twin cohort was established in 1986 and consists of all twin pairs (including opposite-sex pairs and parents of twins) born in Finland during 1958-1986. The latter comprise of 21,958 twin pairs (6,114 MZ, 7,922 SSDZ and 7,922 pairs of OSDZ) identified from Finland's Central Population Registry (Kaprio et al. 1990). For twins born from 1974 onwards, the number of twins identified from the Central Population Registry is nearly identical with the number of twins born annually according to birth statistics compiled by the Central Statistical Office of Finland (Kaprio et al. 1990).

FinnTwin16

The FinnTwin16 is a longitudinal study of five consecutive birth cohorts of Finnish twins, their siblings and parents. For the FinnTwin16, twins of the younger twin cohort born in 1975 through 1979 were identified. Questionnaires were mailed to twins within two months of their 16th birthday inquiring about similarity in appearance, health habits, and symptoms, as well as personality and social relationships. All respondent twins are again surveyed at ages 17, 18.5, and 21 years. The goal of this ongoing study is to carry out analyses of genetic and environmental contributions to consistency and change in health-related behaviours, as described in more detail by Rose et al (1999) The study is a Finnish-American collaborative study funded by the National Institutes of Health of the USA.

The population of the present thesis consists of the twins and their parents of the FinnTwin16. The study population in each of the original communications varied according to the degree of completed baseline data collection at the time of the analysis as shown in Figure 1.

Figure 1. Number of twin pairs in each original communication.



Data collection

The baseline data collection for FinnTwin16 took place from 1991 through 1995. Simultaneously with the baseline assessment of the twins, the parents of the twins were mailed a family questionnaire about the birth, development, and growth of the twins through childhood, and adolescence until age sixteen. Questions were included on chronic conditions and diseases such as asthma and hay fever in the twins. Each parent was also asked to reply to a personal questionnaire on his/her own health and lifestyle, including questions on asthma and hay fever.

Zygosity determination

Twin zygosity was determined by examining the responses of both members of each twin pair to questions on their similarity in appearance at primary-school age (Appendix I, questions 6-8). By using a set of decision rules (Sarna et al. 1978), the twin pairs were classified as MZ, DZ, or of undetermined zygosity. This method has been validated among twins aged 18 or older by use of 11 genetic markers (Sarna et al. 1978). Twins of undetermined zygosity were classified by discriminant analyses using the data transformations and an analytic approach described by Sarna and Kaprio (1980).Additional information such as photographs, fingerprints, and DNA-marker studies were used for zygosity determination when needed. At present, uncertainty about zygosity remains for 3.6% (N=101) of the pairs. Twins were classified by zygosity and sex as female monozygotic (FMZ), male monozygotic (MMZ), female same-sexed dizygotic (FSSDZ), male same-sexed dizygotic (MSSDZ), opposite-sex dizygotic (OSDZ), and of undetermined zygosity (XZ).

VARIABLE DEFINITION

Outcome variables

Asthma in the adolescents was defined on the basis of the parental response in the family questionnaire on whether the first-born twin, the second-born twin, neither, or both of the twins had been diagnosed with asthma. If asthma status of a twin could not be determined by the response, asthma data on that twin were regarded as missing. Hay fever in the twin was defined in a similar fashion (Appendix II, question 10).

Disease status of the parents

The parents were asked, 'Has a doctor ever said or do you have or have you ever had any of the following'. The list included 'allergic rhinitis, e.g. hay fever' and 'asthma' (Appendix III, question 13).

Perinatal variables

In the family questionnaire, the parents were asked to state the birth weight, length at birth, and Apgar score of each twin, in which gestation week the twins were born, and whether the twins had to stay in hospital after birth and for what reason (Appendix II). The data on perinatal measures were examined for outliers and rechecked if necessary from the original questionnaires

Ponderal index was calculated as birth weight (kg) divided by the cube of birth length (m^3) (Cole et al. 1997). Gestation-adjusted birth weight was calculated by subtracting from the twin's birth weight the mean birth weight of all twins born in the same week of gestation and dividing this difference by the latter. This variable was then divided into fifths and grouped into three categories (lowest fifth, second-to-fourth fifth, highest fifth). The age of the mother at the birth of the twins was calculated by subtracting her birth year from the twins' year of birth.

Non-perinatal variables

Gender, parental asthma and hay fever, number of older siblings, father's occupation, parental smoking, and the adolescent's own smoking were chosen as possible non-perinatal risk factors for logistic regression analysis of asthma (IV) and hay fever (V). The effect of sibship size was also studied separately in more detail (III).

The number of older siblings of the adolescents was determined by the mother's response on the question inquiring whether she had children older than the twins, and if yes, how many (Appendix III, question 5). Due to the small number of families with three or more older siblings, these were grouped (III). For the logistic regression analysis, families were put into two groups (0-1 siblings and 2 or more siblings) because the occurrences within the groups were similar.

The parents furnished data in personal questionnaires on their occupations, smoking habits, and practice of smoking indoors for the period when the twins were under school age (Appendix III). A detailed smoking history was obtained from the parents, but Study IV used dichotomised smoking variables (Aarnio et al. 1997)ADDIN. Parents who had smoked fewer than 5-10 packs of cigarettes during their whole lives were classified as non-smokers, and those who had smoked more were regarded as ever-smokers (Vesterinen et al. 1988). Environmental tobacco smoke exposure was considered present if the mother reported that at least one person had smoked indoors at home when the twins were under school age (in Finland age seven). In Study V, information on parental smoking was combined into one variable in three categories (both parents non-smokers, at least one parent a smoker but no environmental tobacco-smoke exposure reported, environmental tobacco-smoke exposure reported).

Information on the twins' smoking habits was drawn from their personal questionnaires (Appendix I, questions 20-22). Those adolescents who had never smoked or had smoked at most 50 cigarettes during their lives were classified as non-smokers and otherwise as smokers at the age of 16.

The father's occupation at the time of the survey was grouped according to the classification of Statistics Finland: (1) farmers, (2) other self-employed persons, (3) upper-level employees, (4) lower-level employees, (5) manual workers, and (6) others including students and pensioners (Aarnio et al. 1997).

STATISTICAL METHODS

Occurrence of asthma and hay fever in twin families

On the basis of the formulation of the questions on asthma and hay fever, doctor-diagnosed life-long disease occurrences, equivalent to cumulative incidence, could be obtained on both twins and the parents. Cumulative incidences for the twins were calculated also stratified by zygosity and sex, and they were compared by tests of homogeneity of prevalence rates (Kirkwood 1988). Twin similarity was assessed with the probandwise concordance rate, i.e. the number of affected individuals in pairs where both are affected as a proportion of all the affected, (Plomin et al. 1990, Falconer and MacKay 1995) and tetrachoric correlations (with 95% CI) computed from pairwise contingency tables (2x2 table indicating the number of pairs where neither is affected, either the A-twin, or the B-twin, or both are affected). Tetrachoric correlation is the within-pair correlation of a

dichotomous trait, assuming underlying normal distribution (Neale and Cardon 1992). The parents' similarity for asthma (I) and hay fever (II) was also assessed with tetrachoric correlation. The risk for asthma (I) and hay fever (II) in the offspring was assessed with the rate ratio after stratification of the twin data on the corresponding parental disease status. The effect of parental asthma (I) and hay fever status (II) on the occurrence of the corresponding disease in their offspring was examined for each parent separately and independently of the other parent's disease status.

Genetic modelling

Model fitting is carried out to estimate the components of variance in the liability to the trait studied. The model assumes that the disease is polygenic and multifactorial, and the liability to the disease is normally distributed (Falconer and MacKay 1995). The disease becomes manifest when a certain level or threshold of liability is reached. These assumptions were considered reasonable for two reasons. Firstly, the tetrachoric correlations for asthma (I, Table 1) and hay fever (II, Table 1) in MZ twins were considerably less than unity and less than twice that in DZ twins, indicating that the genetic effects were probably additive (Neale and Cardon 1992). Secondly, no single major gene controlling the expression of either asthma or atopy has been identified thus far (Holgate 1997). Modelling was also carried out on twin data stratified by parental disease status.

From data on twins reared together, it is possible to model four separate parameters: an additive genetic (A) component and effects due to dominance (D), as well as common (C), and unique (E) environmental components. Common (also called shared) environmental effects are those shared by both twins or all family members, while unique environmental effects are uncorrelated between family members and represent the exposures of each individual. One can fit models based on the different combinations of these parameters: AE, ACE, ADE, and CE (Falconer and MacKay 1995). Heritability is the sum of additive (A) and non-additive (D) genetic effects as a proportion of total variance.

Variance component estimates were calculated based on information in the contingency tables in different zygosity groups (MZ and DZ); χ^2 goodness-of-fit statistics were used to assess how well a model fits the data. The goodness-of-fit of alternative, hierarchically nested models can be compared by their difference in χ^2-values. The χ^2-difference is itself χ^2-distributed and its degree of freedom is the difference in degrees of freedom of the models being compared. The Akaike

Information Criterion (AIC) is a global measure of goodness-of-fit calculated by subtracting twice the degrees of freedom from the χ^2 (Neale and Cardon 1992).

Environmental risk factors

Sibship size effect

The cumulative incidence of hay fever and asthma in the adolescents according to number of older siblings was calculated first among all adolescents. Differences in cumulative incidences were calculated with 95% CIs, and significance for trend with increasing number of siblings was assessed by Cochran's χ^2-test for trend (Cochran 1954). Additionally, in order to repeat the analysis on independent observations, a similar analysis was performed for hay fever among adolescents randomly chosen one from each pair.

Logistic regression

Odds ratios for asthma in the adolescents were calculated separately for perinatal and non-perinatal variables. For the adjusted regression models, cases with data available on all factors in each model were included. Because genetic modelling showed heterogeneity in liability especially to asthma by parental disease status (I), a similar analysis was performed also on data stratified by corresponding parental disease status: families with at least one parent affected and families where neither parent had the disease. Because in only a few families, both parents were affected, in most analysis these were pooled with families with only one affected parent. Adjusted ORs were obtained by including possible confounders in the analysis (IV, V). Finally, those perinatal and non-perinatal risk factors with significant or nearly significant Wald statstics were included in a single model, and backward stepwise logistic regression was performed in order to obtain the most parsimonious model.

The test for trend within variables with several categories was performed by logistic regression. Each category with an assigned rank (1, 2, …) was entered in the model as a continuous variable. The Wald statistic thus obtained served as the test statistic, with its significance level being used to assess significance for trend. Because individual observations on twins selected as pairs may not be regarded as totally independent, generalised estimating equations (GEE) were used in the regression analysis in order to correct for any lack of independence (SAS Proc Genmod) (Liang and Zeger 1986).

Population-attributable proportion

The population-attributable proportion expresses the proportion of the disease due to exposure to the risk factor analysed for all cases, whether exposed or unexposed (Rothman 1986). Since the attributable proportion combines information on both the magnitude of the risk and the prevalence of the risk exposure, it gives an estimate of the impact of the risk factor at the population level.

Discordant pair analysis

MZ and DZ pairs discordant for asthma (IV) and hay fever (V) were identified. Within these pairs separately for MZ and DZ, birth weight, ponderal index, and Apgar score among the affected twins were compared to the corresponding values among unaffected co-twins by the Wilcoxon signed rank test (Kirkwood 1988). In a similar fashion, categorised birth weight, ponderal index, gestation-adjusted birth weight, and neonatal hospitalisation in affected co-twins were compared to these factors in unaffected co-twins by McNemar's two-sided test (Kirkwood 1988).

Statistical software

Analyses were done with SPSS, Release 7.5.1. and SAS, Release 6.12. Genetic modelling analyses were carried out with Mx (versions 1.40 & 1.47), a statistical program for genetically informative data sets (Neale 1991).

RESULTS

The overall response rate for girls was 93%, for boys 88%, for mothers, 87%, and for fathers 84%. The family questionnaire was returned by 87% of the families.

OCCURRENCE OF ASTHMA AND HAY FEVER

Asthma was reported for 4.6% of the boys and for 3.6% of the girls (Table 6a) and hay fever for 15.1% and for 10.1% (Table 6b). The gender differences were significant, whereas no difference appeared in cumulative incidence by twin type. MZ twin pairs were significantly more concordant for both asthma and hay fever than were DZ twin pairs, whereas no difference appeared in concordance rates between opposite-sex and like-sexed DZ twin pairs judged by the probandwise concordance rates (I & II, Table 1). A MZ co-twin of a twin with asthma had an eleven-fold risk for asthma compared to that of the population at large, while for a DZ co-twin the risk was five-fold (I). The corresponding risk for hay fever in a MZ twin with an affected co-twin was five-fold and that of a DZ twin three-fold (II).

Asthma was reported by 4.6% (n=194) of mothers and by 3.5% (n=150) of fathers, yielding a total occurrence of 4.1% in parents. Mothers also reported hay fever (18.1%, n=776) more often than did fathers (14.8%, n=640) (16.4% among all parents). The parents were somewhat more similar for both asthma and hay fever than would have been expected on the basis of random association alone as judged by the tetrachoric correlations (0.27 for asthma, 95% CI 0.08-0.46 and 0.24 for hay fever, 95% CI 0.15-0.35) (I, II).

Asthma was reported for 11% of the children of asthmatic mothers and 10% of those of asthmatic fathers, while only 3% of the children of non-asthmatic parents had asthma (I, Table 2). Hay fever occurred in 17% of the children of mothers and 15% of fathers with hay fever, but in only 7% of children of parents without hay fever (II, Table 2). Because there was no significant difference in the risk for either asthma or hay fever between boys and girls, the data for both sexes were pooled to yield a common risk estimate. The risk for a child to be asthmatic was four-fold, if either the mother or father had asthma compared to risk of children with non-asthmatic parents (I, Table 2) whereas if either the mother or father had hay fever, the risk for their twin offspring's having hay fever was two-fold that of a twin with unaffected parents (II, Table 2).

Table 6a. Cumulative incidence of *asthma* among Finnish adolescent twins by gender and zygosity type.

Zygosity	**Cumulative incidence of asthma in adolescents % (n)**			
	No. of adolescents	**Neither parent asthmatic (N=3392)**	**Either parent with asthma (N=290)**	**All**
MZ girls	664	2.5% (15)	6.7% (4)	2.9% (19)
DZSS girls	584	2.2% (12)	22.5% (9)	3.6% (21)
DZOS girls	625	3.5% (20)	15.4% (8)	4.5% (28)
XZ girls [a)]	44	2.5% (1)	0% (0)	2.3% (1)
All girls	**1917**	**2.7% (48)**	**13.5% (21)**	**3.6% (69)**
MZ boys	466	3.5% (15)	26.3% (10)	5.4% (25)
DZSS boys	582	4.8% (26)	8.3% (3)	5.0% (29)
DZOS boys	625	2.6% (15)	17.3% (9)	3.8% (24)
XZ [a)]	92	3.6% (3)	0% (0)	3.3% (3)
All boys	**1765**	**3.6% (59)**	**16.4% (22)**	**4.6% (81)**
Total	**3682**	**3.1% (107)**	**14.8% (43)**	**4.1% (150)**

a) XZ = unknown zygosity

Table 6b. Cumulative incidence of *hay fever* among Finnish adolescent twins by gender and zygosity type.

Zygosity	**Cumulative incidence of hay fever in adolescents % (n)**			
	No. of adolescents	**Neither parent with hay fever (N=2788)**	**Either parent with hay fever (N=1150)**	**All**
MZ girls	726	7.5% (37)	17.7% (41)	10.7% (78)
DZSS girls	604	6.4% (30)	15.4% (21)	8.4% (51)
DZOS girls	667	8.1% (39)	16.8% (31)	10.5% (70)
XZ girls [a)]	56	13.9% (5)	15.0% (3)	14.3% (8)
All girls	**2053**	**7.5% (111)**	**16.8% (96)**	**10.1% (207)**
MZ boys	504	13.9% (47)	19.3% (32)	15.7% (79)
DZSS boys	616	10.4% (44)	22.9% (44)	14.3% (88)
DZOS boys	667	10.1% (49)	30.4% (56)	15.7% (105)
XZ [a)]	98	4.8% (3)	25% (9)	12.2% (12)
All boys	**1885**	**10.9% (143)**	**24.4% (141)**	**15.1% (284)**
Total	**3938**	**9.1% (254)**	**20.6% (237)**	**12.5% (491)**

a) XZ = unknown zygosity

GENETIC MODELLING

Asthma

Among twins with *at least one asthmatic parent*, genetic effects accounted for 87% and unique environmental effect for 13% of variance in the most parsimonious model (AE) (I, Table 4). In the less parsimonious ACE model, the estimate for common environment was zero, and thus the proportions of genetic and unique environmental effects were equal to those in the AE model. Both models including only environmental effects (CE and E) could be rejected (I, Table 4).

In the twin pairs with *non-asthmatic parents,* environmental factors accounted for a higher proportion of variance in susceptibility to asthma than among twins with asthmatic parents (I, Table 5). And in contrast to the first group, the CE model including only environmental effects explained the twin data equally well. Due to the low occurrence of asthma among the offspring of non-asthmatic parents, no further distinction between the AE, ACE, and CE models was possible. The model comprising unique environmental effects (E) alone could be rejected (I, Table 5).

A test of heterogeneity on AE models indicated that a model with the same genetic and environmental effects could not explain the development of asthma in both sets of families (χ^2 = 34.91, degrees of freedom =2, P<0.0001) (I).

Hay fever

Similar to asthma, in families with *a parental history of hay fever*, both the AE and the ACE model accounted for the data equally well, and the fit of the CE model was significantly worse, as judged by AIC (Table 7). The model comprising only unique environmental effects (E), could be rejected. The heritability estimate for hay fever in these families was 77%.

Among twin pairs with *no parental history of hay fever*, genetic components of variance were needed to explain the data, because the CE model gave a significantly worse fit (Table 7). Again, the model comprising only E could be rejected.

However, heterogeneity testing suggested differences in variance between the families (difference in χ^2 55.2, degrees of freedom =2, p<0.0001), which may be

Table 7. Results of genetic modelling on hay fever data stratified by parental hay fever status among Finnish adolescent twins. [a)]

Data on hay fever in the adolescents								
No hay fever in parents					**At least one parent with hay fever**			
Model	**Components of variance estimates**			**AIC** [b)]	**Components of variance estimates**			**AIC** [b)]
	Additive genetic effects (A)	Shared environment (C)	Unique environment (E)		Additive genetic effects (A)	Shared environment (C)	Unique environment (E)	
ACE	0.67	0.13	0.20	-3.20	0.77	0.00	0.23	-0.52
AE	0.82	—	0.18	-4.71	0.77	—	0.23	-2.52
CE	—	0.59	0.41	3.12	—	0.50	0.50	6.60
E	—		1.0	66.2	—	—	1.0	35.6

a) Modelling based on 16 concordant, 26 discordant, and 287 unaffected MZ pairs; and 18 concordant, 92 discordant, and 644 unaffected DZ pairs with no parental history of hay fever; and 15 concordant, 20 discordant, and 112 unaffected MZ pairs; and 21 concordant, 74 discordant, and 173 unaffected DZ pairs with parental history of hay fever.
b) AIC = Akaike Information Criterion

due to different thresholds for hay fever in families either with or without hay fever in the parents.

ENVIRONMENTAL RISK FACTORS

Asthma

Perinatal variables

Logistic regression analysis on all adolescents

In the univariate analysis of categorised perinatal variables, risk for asthma increased with increasing ponderal index (p for trend <0.01) and decreasing maternal age (p for trend <0.01) (IV, Table 2). Among those in the highest fourth of the ponderal index, the risk for asthma was 82% higher than for those in the lowest fourth. Assuming the median birth length (47 cm), the mean ponderal index in the lowest and highest groups corresponded to length-adjusted birth weights of 2260 g and 2970 g. This, in turn, corresponds to an approximately 10% increase in risk per 100 g increase in birth weight. After adjustment for confounding variables, a high ponderal index remained a significant risk factor (p for trend <0.05; OR for the highest fourth 1.86, 95% CI 1.13-3.07) (IV, Table 2). The offspring of mothers under 25 years of age were at significantly higher risk for developing asthma than were those of older mothers (unadjusted OR 0.62, 95% CI 0.41-0.94) (IV, Table 2).

Logistic regression analysis stratified by parental asthma status

Testing suggested interactions between parental asthma status and categorised ponderal index (P for Wald statistic of the interaction term = 0.08) and gestation-adjusted birth weight (categorised as continuous P=0.04 and categorised P=0.10) (IV). Among adolescents with *non-asthmatic parents*, the risk for asthma in adolescents increased with increasing ponderal index (Table 8; P for trend <0.01 when adjusted for confounders, IV). Among adolescents with *asthmatic parent(s)*, a similar trend of increasing asthma risk was found for gestation-adjusted birth weight (Table 8; P for trend <0.01 when adjusted for confounders, IV). Those with a higher ponderal index also had a higher risk for asthma than did those with the lowest ponderal index (Table 8). However, there was no

significant trend, and CIs included unity as their being few cases in each category.

Discordant pair analysis

Among asthma-discordant MZ pairs (32 pairs), twins with asthma tended to have a lower birth weight, lower ponderal index, and lower Apgar score than did their unaffected co-twins, whereas among asthma-discordant DZ pairs (101 pairs), twins with asthma had a higher birth weight and ponderal index than their unaffected co-twins. In ponderal index, the difference among DZ discordant pairs was significant ($p<0.05$), but the differences between MZ and DZ pairs were not (IV, Table 5). Neither were there significant associations between categorised birth weight, ponderal index, gestation-adjusted birth weight, or neonatal hospitalisation and disease status in the asthma-discordant pairs overall or stratified by zygosity (IV).

Non-perinatal variables

No significant difference could be observed in cumulative incidence of asthma by the number of older siblings (III, Table 1). However, in univariate logistic regression analysis, all non-perinatal variables were associated with asthma. When non-perinatal variables were included in the same model, parental asthma, maternal smoking, and sibship size remained the strongest determinants of asthma (IV, Table 3). There were no significant interactions between parental asthma status and non-perinatal variables.

Perinatal and non-perinatal variables combined

When significant perinatal and non-perinatal risk factors were combined in a single logistic regression model, the following remained independent determinants of asthma: ponderal index, maternal smoking, number of older sibs, and parental asthma (IV, Table 4). In the model, additionally adjusting for hay fever in the adolescent showed a similar result except for sib ship size which was replaced by neonatal hospitalisation (OR 1.60, 95% CI 1.00-2.47) (IV). The highest attributable proportions were assigned to sibship size (32%), maternal smoking (25%), and parental asthma (32%). However, the attributable proportion of ponderal index was not much smaller than that of parental asthma (IV, Table 4).

Hay fever

Perinatal variables

Logistic regression on all adolescents

Significant trends for increasing risk for hay fever ran parallel to increasing birth weight (P<0.05, before and after adjustment for confounders) and with increasing gestational age (P<0.05, after adjustment for confounders; OR for those born >40 wk of gestation was 2.24, 95% CI 1.03-4.86) (V). Additionally, the risk for hay fever was significantly lower among those who had been hospitalised after birth (unadjusted OR 0.80, 95% CI 0.65-0.99, adjusted OR 0.74 95% CI 0.58-0.94). Of the hospitalisations, 63% were reportedly due to prematurity (V).

Logistic regression analysis stratified by parental asthma status

Among the adolescents with *no parental history of hay fever*, there was a significant trend for higher risk for hay fever with increasing birth weight and ponderal index (P for trend <0.05, when adjusted for confounders) (Table 8 & V, Table 2). The trend with increasing unadjusted ponderal index, gestational age, and gestation-adjusted birth weight was similar but did not quite reach statistical significance (P for trend =0.07, Table 8). Among adolescents with *a parental history of hay fever*, no significant associations between perinatal variables and hay fever risk were evident (Table 8). Only those born post-term were at higher risk for hay fever than were those born very preterm when adjusted for confounders (OR 5.07, 95% CI 1.40-18.4) (V, Table 3). The tendency towards higher risk for hay fever with increasing gestational age was observed in both sets of families.

Discordant pair analysis

Within twin pairs discordant for hay fever, MZ twins (68 pairs) with hay fever weighed 15 grams more (median) than their unaffected co-twins, whereas DZ twins (253 pairs) with hay fever weighed 30 grams more than their unaffected co-twins (V). However, no statistically significant differences were observed between affected and unaffected co-twins in continuous or categorised birth weight, ponderal index, gestation-adjusted birth weight, Apgar score, or neonatal hospitalisation (V).

Non-perinatal variables

Cumulative incidence of hay fever among adolescents with three or more older siblings was significantly lower than among those with either none, one, or two siblings (III, Table 1). This result remained even when only one twin of each twin pair was analysed, and also this trend towards a decline in occurrence of hay fever with greater number of older siblings was significant (III, Table 1).

In univariate logistic regression analysis, all non-perinatal variables were associated with hay fever (V, Table 5). After multivariable adjustment, parental hay fever, sibship size, father's occupation, and gender remained significant determinants of adolescents' hay fever (V, Table 5).

Perinatal and non-perinatal variables combined

When included in a single model, neonatal hospitalisation, gender, parental hay fever, sibship size, father's occupation, and parental smoking remained independent determinants of hay fever in these adolescents (V, Table 6). Gestation-adjusted birth weight was not included in the model, due to its correlation with birth weight. The highest attributable proportions could be assigned to the father's occupation (39%), sibship size (25%), and parental hay fever (24%) (V, Table 6).

Table 8. Perinatal risk factors for asthma and hay fever in 16-year-old Finnish adolescent twins by parental disease status. Crude ORs with 95% CIs.

		Data on asthma in adolescents					Data on hay fever in adolescents				
		No asthma in parents (N=3392)			Asthma in parents (N=290)		No hay fever in parents (N=2788)			Hay fever in parents (N=1150)	
Perinatal risk factors		**N**	**OR**	**95% CI**	**OR**	**95% CI**	**N**	**OR**	**95% CI**	**OR**	**95% CI**
Birth weight	<2000	379	1.0		1.0		404	1.0		1.0	
(g)	2000-2499	851	0.75	0.36-1.58	1.02	0.29-3.60	913	1.09	0.65-1.82	0.83	0.49-1.39
	2500-2999	1403	0.66	0.33-1.32	0.70	0.21-2.34	1508	1.25	0.78-2.03	1.08	0.65-1.79
	≥ 3000	996	0.93	0.46-1.88	1.25	0.38-4.13	1058	1.58	0.97-2.59	0.95	0.55-1.63
Test for trend			P=0.9		P=0.8			P=0.03		P=0.9	
Ponderal	Lowest ¼	889	1.0		1.0		954	1.0		1.0	
index	2nd ¼	877	0.66	0.36-1.21	2.05	0.75-5.59	939	1.16	0.80-1.69	0.86	0.57-1.29
in fourths	3rd ¼	887	0.89	0.51-1.56	1.08	0.36-3.23	954	1.34	0.92-1.95	0.79	0.52-1.18
	Highest ¼	900	1.50	0.89-2.53	2.14	0.79-5.81	950	1.38	0.95-2.00	0.90	0.60-1.35
Test for trend			P=0.07		P=0.3			P=0.07		P=0.4	
Gestational	< 33	232	1.0		1.0		252	1.0		1.0	
age (weeks)	33-36	946	0.85	0.33-2.20	0.49	0.11-2.09	996	0.86	0.46-1.62	1.18	0.55-2.53
	37-40	1964	1.04	0.43-2.54	0.32	0.08-1.34	2100	1.29	0.72-2.29	1.15	0.56-2.35
	>40	92	1.12	0.27-4.58	1.50	0.17-13.3	104	1.33	0.47-3.73	3.02	0.94-9.67
Test for trend			P=0.6		P=0.5			P=0.07		P=0.3	
Gestation-	Lowest 1/5	632	1.0		1.0		672	1.0		1.0	
adjusted birth	2nd-4th 1/5	1932	0.79	0.47-1.32	2.82	0.82-9.73	2076	1.41	0.99-2.03	0.99	0.65-1.49
weight	Highest 1/5	635	1.00	0.53-1.89	4.55	1.26-16.4	671	1.54	0.97-2.44	0.97	0.57-1.63
in fifths											
Test for trend			P=1.0		P=0.01			P=0.07		P=0.5	
Maternal age	<25	1136	1.0		1.0		1210	1.0		1.0	
at birth of	25-30	1466	0.71	0.43-1.15	0.57	0.23-1.40	1574	1.11	0.78-1.60	0.93	0.64-1.36
twins (years)	>30	1080	0.61	0.36-1.05	0.66	0.29-1.51	1154	1.09	0.74-1.60	0.80	0.52-1.22
Test for trend			P=0.07		P=0.3			P=0.6		P=0.2	

DISCUSSION

STUDY POPULATION AND METHODS

The study population, five consecutive birth cohorts of 16-year-old twins and their parents, both with high response rates, is unique. Since all twins were assessed at the same age, the data do not allow for assessment of age-related effects. On the other hand, no age-adjustment was needed. Choosing consecutive birth cohorts minimises possible cohort effect. Because the FinnTwin16 assessed multiple aspects of the health and behaviour of adolescents, bias towards over-reporting of asthma and hay fever is unlikely. Apart from forming a large twin sample, the study population consisted of Finnish adolescents nation-wide, unselected except for twinship.

Whether twins are representative of the population in general depends on how much being a twin affects the trait studied. With twins, the main concerns are prenatal circumstances and common rearing environment (Parisi 1995). Differences between twins and singletons in intrauterine life would presumably be reflected in the occurrence of the studied trait also between MZ and DZ twins because these differ in placentation and chorionicity (Martin et al. 1997). The more similar environment in MZ twins than in DZ twins may cause an overestimation of genetic effects (Kyvik 2000). However, greater similarity in rearing practices and infant care in MZ has been overestimated (Kyvik 2000). Representativeness of twins in this study is discussed for each variable separately.

Questionnaire diagnosis of asthma has been shown to be a valid and reproducible method for epidemiological studies (Burney et al. 1989, Tóren et al. 1993). In young Finnish adults, a question on doctor-diagnosis of asthma has shown high positive predictive value (0.82), specificity (0.99), and lower sensitivity (0.36) when validated against the doctor's interview and objective measurements (Kilpeläinen et al. in press). A question on doctor-diagnosed nasal allergy or hay fever proved almost equally valid: positive predictive value 0.76, specificity 0.93, and sensitivity 0.52 (Kilpeläinen et al. in press). In this study, asthma and hay fever were defined by parental report of doctor-diagnosed disease. This may result in lower occurrences with more severe cases compared to a symptom-based definition. Defining allergic rhinitis as hay fever excludes those with perennial rhinitis with no distinct exacerbation of rhinitis symptoms during the pollen season and possibly some of those with seasonal rhinitis triggered by pollen other than grass, even though hay fever and seasonal allergic rhinitis are often used as

synonyms (Charpin et al. 1996). This definition may also lead to lower occurrence. However, when assessing risk, this is not as harmful as overestimating the occurrence, because it leads to underestimation of the true associations rather than overestimating (Tóren et al. 1993).

Since the question on rhinitis in FinnTwin16 was formulated slightly differently for twins and parents ('hay fever' vs. 'allergic rhinitis, e.g. hay fever'), the definitions may not totally correspond with each other yielding a some what wider range of rhinitis in the parents. This may lead to relatively higher cumulative incidence figures in parents and underestimating the associated risk factors.

Defining asthma by doctor diagnosis ever without further data on age of onset or present symptoms does not allow for a distinction between past, current, or persistent asthma, such as those phenotypes suggested by Martinez et al. (1995). However, in Finland in the early 1980's, obstructive bronchitis in children under three years of age was defined separately from asthma, even though in clinical practice the distinction may not have been easy (Backman 1984).

RESULTS

Occurrence of asthma and hay fever in twin families

The cumulative incidences of asthma and hay fever in this study are comparable to those recently reported in Finnish singletons of the same age (Varjonen et al. 1992, Rimpelä et al. 1995). The slightly higher one-year prevalences among 13- to 14-year-olds participating in the ISAAC study are to be expected, because of the symptom-based definition used in that study (Pekkanen et al. 1997, Remes et al. 1998). Additionally, other twin studies on asthma and hay fever reporting similar rates of asthma and hay fever among twins and among singletons suggest that, in respect to theses diseases, twins may be representative of the general population (Harris et al. 1997, Skadhauge et al. 1999). However, in a study on perinatal risk factors, multiple birth (to be born as a twin, triplet, etc.) decreased the risk for both hay fever and asthma among Swedish conscripts, and a lower prevalence of wheezing among twins than among singletons has been suggested (Michie et al. 1996). On the other hand, there was no difference in the prevalence of asthma or hay fever between twins and singletons included in the older Finnish Twin Cohort (E. Huovinen, personal communication). Comparative

epidemiological studies would be needed to show whether differences in prevalence of allergic disease exist between twins and singletons.

The excess of both asthma and hay fever in boys was expected because we used cumulative incidence, which reflects the higher disease occurrence in boys in childhood (Remes et al. 1996, Harris et al. 1997, Lichtenstein and Svartengren 1997, Pekkanen et al. 1997).

Among parents of twins, cumulative incidence of asthma was similar to that reported earlier in Finland (Heinonen et al. 1987), but occurrence of hay fever was lower than the previously reported symptom-based prevalence of allergic rhinitis, and higher than the doctor-diagnosed prevalence of hay fever (Luoma and Koivikko 1982, Heinonen et al. 1987). While prevalence of atopic disorders among children and adolescents has been the subject of several studies recently in Finland, there is an apparent lack of corresponding studies among adults.

The four-fold higher risk for asthma among adolescents with asthmatic parent(s) and two-fold higher risk for hay fever among adolescents with hay fever in their parents correspond to risk estimates in other family studies (Dold et al. 1992, Diepgen and Blettner 1996, Jenkins et al. 1997, Rona et al. 1997). We found no difference in risk either by gender of offspring or by gender of parent, as is suggested in some studies (Fergusson et al. 1983, Dold et al. 1992, Litonjua et al. 1998). This may be due to sample size or symptom perception, but in questionnaire studies bias may arise also due to mothers alone reporting on disease status for the whole family. In our study this was minimised, since each parent was mailed his/her own personal questionnaire. However, studies applying objective measures of atopy have suggested a stronger maternal effect on atopy, atopic dermatitis, serum IgE, and pulmonary function (Cookson et al. 1992, Ruiz et al. 1992, Givelber et al. 1998, Holberg et al. 1998)ADDIN.

Risk for a disease between DZ twins is genetically comparable to risk between siblings, whereas environmental correlation within a pair of twins may be higher than that between siblings. The higher risk for asthma (five-fold) and hay fever (three-fold) based on having an affected sibling rather than an affected parent — also observed in other studies (Hopper et al. 1990, Diepgen and Blettner 1996) — may be due to dominance, i.e., interaction between alleles at same locus, epistasis, i.e., interaction between alleles at different loci, or to a cohort effect.ADDIN

Genetic modelling

Heritability estimates of asthma are relatively high (62%-79%) and surprisingly similar in different second generation studies irrespective of the age of the study subjects (Table 1). However, studies including only twin pairs reared together may overestimate the genetic component, because non-additive genetic effects cannot be accounted for in the presence of a shared family environment (Neale and Cardon 1992). Measurement errors, for example, in the classification of the disease, will increase the unique environmental component. Another finding common to recent twin studies is the negligible proportion of shared family environment in the variability (Table 1). However, the classic twin method may lack the statistical power to detect shared environmental effects, especially if the equal environment assumption is violated by the greater similarity of MZ twins (Hopper 2000). Our significant correlation in asthma between spouses (0.27) and the preliminary report of an adoption study would suggest that a within-family shared component would exist (Smithe et al. 1998). Further study using measurements of family environment might prove very helpful.

Additionally, our result suggests heterogeneity in the variance components according to family history. In families in which neither parent had asthma, in addition to models comprising additive genetic effects, the model comprising only environmental effects fitted the data equally well. This supports the idea that genetic and environmental influences play different roles in different subjects (Martinez 1998), and that asthma is a genetically heterogeneous disease.

The heritability estimates for hay fever were of the same magnitude as those for asthma, but additive genetic effects were needed to explain the data in both sets of families (Table 7). This may be due to the higher statistical precision with larger numbers of affected. It may also suggest that environmental factors influence the expression of hay fever less than that of asthma in subjects with no family history of disease. This would appear plausible when considering allergens associated with these diseases (Sears et al. 1993).

Interestingly, heritability estimates for certain biochemical measurements derived from twin studies have proved equal to the amount of variance accounted for by polymorphisms found in the causative genes (Martin et al. 1997). The high heritability of asthma and hay fever in recent twin studies offer evidence that influential susceptibility genes for these traits do exist.

Perinatal risk factors

Because the Finnish Medical Birth Registry was not launched until 1987, we had to rely on parental reporting of birth data. Compared to register-ascertained birth data, reported birth data is less complete, and there may well be inaccuracies because of parents' recalling birth measures dating back 16 years. However, maternal reports of birth weight and gestational ages have shown very good agreement with medical records (Seidman et al. 1987), and birth weights of the twins participating in the study are well in accordance with the birth statistics of multiples born in Finland during that period (Anonymous 1980).

Several studies have observed a negative association between birth weight and asthma (Table 6), but we could not confirm this among twins, although those at the extremes of birth weight had slightly higher ORs than did those with intermediate birth weights (IV, Table 2). Growth retardation in the third trimester of pregnancy is a common cause of lower birth weight in twins (Kaprio and Pietiläinen 1999). However, maturation, especially of the lungs and central nervous system, takes place at the same stage of pregnancy in twins as in singletons — if not earlier — and for most twins the catch-up growth after birth is rapid and is complete by school age (Wilson 1979, Amiel-Tison and Gluck 1995). In singletons, low birth weight is more often due to premature birth. Prematurity with its pulmonary complications contributes to the increased risk for wheezing illness, particularly in childhood (von Mutius et al. 1993). One would expect to find a higher rate of asthma among twins if birth weight in itself was a cause of asthma. Because this was not observed, birth weight is therefore possibly an indicator of another underlying cause for asthma, or there may be mechanisms in the maturation and growth of twins which are protective against the development of asthma.

Over 40% of twins are born preterm, with around half weighing less than 2500 g at birth (Taffel 1995). Because birth weight distribution among twins is different from among singletons, relative measurements of birth weight are probably more descriptive of the intrauterine well-being of twins than is absolute birth weight (Taffel 1995). Ponderal index, length-adjusted body weight, is a measure of fatness or thinness often used as an index of nutritional status at birth. Indeed, the risk for asthma increased with increasing ponderal index also when adjusted for several individual, familial, and social factors (IV, Tables 2 & 4). Only a few studies on the perinatal determinants of asthma have applied adjusted measures of birth weight (Table 6). In the study of Fergusson et al. (1997), the lack of association between ponderal index and asthma may have been due to smaller

sample size and a different distribution of birth characteristics and asthma (13 to 27% had asthma, depending on the definition of asthma).

One possible mechanism for the effect of ponderal index is through obesity, since high ponderal index is associated with obesity and high BMI in adolescence (Rasmussen and Johansson 1998) – and as also was among the twins of this study (K. Pietiläinen, personal communication) — and obesity is associated with asthma and bronchial reactivity (Luder et al. 1998, Shaheen et al. 1999)ADDIN. Shaheen et al. (1999), however, found an association between low birth weight and asthma, and on the other hand, high BMI and asthma at 26 years of age. Longitudinal studies might show possible causal relationships between birth weight, later body weight, and asthma.

Risk for hay fever in this study increased with increasing gestational maturity, which is in keeping with studies among singletons (Table 6 & 8). However, this finding was driven mainly by the higher risk in adolescents with no parental history of hay fever (Table 8). For most variables, the trends or ORs were not statistically significant, but the results of individual variables were consistent with each other (Table 8). The mechanism for increased risk for atopic diseases with gestational maturity is unclear. Since in successful pregnancy the maternal immune system deviates towards the Th2-type cytokine profile (Warner et al. 1996), atopic mothers with the constitutional Th2-type deviation may be able to carry their babies longer towards term (Warner et al. 1996). Another possibility is be that during longer gestation, the baby is be exposed to a longer period of maternal priming of allergic responses (Warner et al. 1998).

The results of discordant pair analysis for both asthma and hay fever should be interpreted with caution, due to the small numbers of discordant pairs. However, the findings among asthma-discordant pairs showing an association between asthma and ponderal index among DZ twins (IV, Table 5) lent support to the similar finding by logistic regression among all adolescents.

Other environmental risk factors

Sibship size

In other studies, as in ours, large sibship, particularly older sibs, appeared protective against hay fever and indicators of atopy (Table 5 & III, Table 1). Large sibship was protective against asthma in study IV but not in Study III, which may be due to the larger number of adolescents in Study IV or the

difference in categorisation of the variable (4 vs. 2 categories). However, the protective effect observed in Study IV (Table 6) disappeared when adjusted for hay fever in the adolescent, suggesting that the effect is mediated through diminished atopic sensitisation.

Twins, even in the absence of other siblings, have one sib, their co-twin. However, young twins are more likely than singleton sibs to share their daily environment and encounter the same antigens at the same time. Thus, twins hardly differ from singletons with respect to the mechanism hypothesis of protective early childhood infections.

Although evidence exists for a lower occurrence of atopic diseases among those with a history of immunologically potent disease (Shaheen et al. 1996, Matricardi et al. 1997, Shirakawa et al. 1997), many studies have failed to show any association between atopic diseases and early childhood infections (Strachan et al. 1996b, Bodner et al. 1998, Farooqi and Hopkin 1998, Pekkanen et al. 1999). As another possible mechanism, Strachan suggested prenatal infections from the mother infected by contact with her older children. However, recent studies have shown a higher risk for atopic diseases among children of mothers who had suffered febrile infections during pregnancy (Xu et al. 1999a, Xu et al. 1999b). The number of older siblings is highly correlated with parity but, in the context of atopy, the possibility of changes in the maternal immunological pattern, with subsequent pregnancies affecting the development of the immunological responses in the fetus, is less well studied.

Farming

We could confirm previous findings of lower risk for hay fever among farmers' children (Kilpeläinen et al. 1997, Braun-Fahrländer et al. 1999) (V, Table 5). This effect was observed also in asthma but diminished after adjustment with adolescent's own hay fever (IV, Table 3). The protective effect of farming appeared to be independent of family size, family history of asthma and hay fever, or smoking (V, Table 5). Whether this association is due to differences in diet or to earlier and more intensive exposure to allergens or antigens in general remains to be shown.

Parental smoking

Maternal smoking was found to be an independent risk factor for asthma (IV, Table 4). Babies of smoking mothers weigh approximately 130 g less than babies of non-smoking mothers (Cliver et al. 1995). This, in addition to postnatal environmental tobacco-smoke exposure predisposes, children to wheezing and asthma particularly in early childhood (Stoddard and Miller 1995, Cook and Strachan 1997b, Cook and Strachan 1997c). Parental smoking in general increased the risk for hay fever in adolescents, whereas reported environmental tobacco-smoke under school age did not. In Finland, with a low prevalence of environmental tobacco smoke exposure at home (Lund et al. 1998), this is probably due to avoidance of smoking indoors, particularly in families with a perceived risk for allergic diseases. With 25% of asthma cases attributable to maternal smoking (IV, Table 4), such smoking is clearly a target for preventive measures (Stoddard and Miller 1995).

SUMMARY AND CONCLUSIONS

The aims of this study were to report occurrence of asthma and hay fever nation-wide among 16-year-old Finnish twins and their parents, to estimate genetic and environmental components of variance in liability to these diseases, and to identify environmental risk factors for asthma and hay fever in relation to family history of these diseases among adolescent Finnish twins.

Among 16-year-old twins, the cumulative incidence of doctor-diagnosed asthma was 3.9% (I) and that of hay fever 12.0% (II) with a higher occurrence of both diseases in boys but no differences between zygosity groups. Among parents of twins, the cumulative incidence of asthma was 4.1% and that of hay fever 16.4%. These figures are in keeping with previous reports from Finland taking into consideration the method used.

The heritabilities of both asthma (76%-87%) (I) and hay fever (77%-82%) (II) were high, but similar to those found in other recent twin studies of children, adolescents, and young adults. In families with no parental history of asthma, variability in liability to asthma among adolescents could be attributed, in addition, to models including genetic factors, to a model including only environmental factors (I). This was in contrast to families with parental asthma, in which additive genetic effects were needed in the model (I).

Of the perinatal factors analysed, high relative birth weight, expressed as ponderal index, and young maternal age increased risk for asthma (IV). In contrast to previous studies, indicators of intra-uterine well-being, but not low birth weight, increased risk for asthma among adolescent twins irrespective of parental asthma status (IV), suggesting that there may be other mechanisms associated with low birth weight that increase risk for asthma rather than low birth weight in itself. Risk for hay fever increased with increasing birth weight and gestational age (V). This was driven primarily by adolescents with no parental history of hay fever (V), suggesting that these effects operate mainly in the absence of genetic predisposition.

Father’s farming occupation and large sibship size were found to be protective against the development of hay fever (V) whereas the mother’s smoking increased the risk for asthma among adolescent twins (IV).

In conclusion, the occurrence of asthma and hay fever among twins is similar to that among singletons, suggesting that the findings from twin studies on asthma

and hay fever may be generalisable to the singleton population. Among adolescents, that both asthma and hay fever show high heritability and only a small effect from shared family environment, implies that genetic factors are the main cause for familial aggregation of these diseases.

These findings as to on perinatal risk factors support previous findings on both atopic and other diseases, in that prenatal environment may affect the susceptibility to disease in later life. Most perinatal risk factors appear similar among twins and among singletons. However, our finding of a higher risk for asthma among those with a high relative birth weight may suggest differences between twins and singletons in prenatal mechanisms affecting asthma risk. First, this finding needs to be evaluated among both twins and singletons. In the case that differences between twins and singletons in perinatal risk factors are confirmed, studies exploring differences in the pre- and postnatal environment between twins and singletons would be indicated.

More detailed studies on the possible pre- and postnatal mechanisms of the protective effect of living on a farm and having a large sibship size may offer explanations for the increase in atopic diseases in developed countries and a further potential for prevention of these diseases. Because smoking, particularly maternal smoking, is a well-established risk factor for childhood asthma, resources should be directed to smoking prevention, particularly among young women.

This study reported the cumulative incidence of asthma and hay fever among two generations of Finns. The genetic contribution to variance in liability to both asthma and hay fever was high. In addition to corresponding parental disease, a high ponderal index at birth and maternal smoking also proved to be risk factors for asthma, while male gender, small sibship and gestational maturity proved to be independent risk factors for hay fever. The relative contribution of genes vs. environment in disease liability and the effect of perinatal risk factors for asthma and hay fever varied according to parental disease status.

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APPENDICES

APPENDIX I

Questions furnishing data for the thesis in the TWIN'S QUESTIONNAIRE
(Numbers relate to the questions in the original FinnTwin16 baseline questionnaire)

1 SEX

1 girl
2 boy

2 DATE OF BIRTH _____/_____19_____

6 IS YOUR TWIN OF THE SAME SEX AS YOU?

1 no ----> go to question 11
2 yes

7 DID YOU AND YOUR TWIN LOOK VIRTUALLY IDENTICAL WHEN YOU WERE ATTENDING THE LOWER GRADES OF SCHOOL, OR DID YOU LOOK NO MORE ALIKE THAN MEMBERS OF A FAMILY USUALLY DO?

1 virtually identical
2 like members of a family usually do
3 Can't say

8 DID YOU AND YOUR TWIN LOOK SO ALIKE DURING YOUR FIRST YEARS AT SCHOOL THAT PEOPLE HAD DIFFICULTY TELLING YOU APART?

1 no
2 yes
3 Can't remember

SMOKING

20 HAVE YOU EVER SMOKED (OR TRIED SMOKING)?

1 no ----> go to question 24
2 yes

HOW OLD WERE YOU WHEN YOU FIRST TRIED SMOKING?
_____years old

0 I have not tried smoking

21 HOW MANY CIGARETTES HAVE YOU SMOKED ALTOGETHER UP TO NOW?

1 none
2 only one
3 about 2-50
4 over 50

22 WHICH OF THE FOLLOWING BEST DESCRIBES YOUR PRESENT SMOKING HABITS?

1 I smoke once or more daily
2 I smoke once or more a week, but not every day
3 I smoke less often than once a week
4 I am trying to or have quit smoking
5 I have never smoked

APPENDIX II

Questions furnishing data for the thesis in the FAMILY QUESTIONNAIRE
(The numbers relate to the questions in the original FinnTwin16 baseline questionnaire)

FIRST WE ASK ABOUT THINGS CONNECTED WITH YOUR PREGNANCY WITH THE TWINS

9. At which week of the pregnancy were the twins delivered? week_____

NEXT WE WILL ASK QUESTIONS RELATED TO THE GROWTH AND DEVELOPMENT OF THE TWINS.

BY CHILD A, WE MEAN THE ONE BORN FIRST; WITH CHILD B, THE ONE BORN SECOND.

1. The Christian names of your twins Child A:_____
Child B:_____

		Child A	**Child B**
2.	Weight at birth	_____gr	_____gr
3.	Length at birth	_____cm	_____cm

4.	Apgar points	_____	_____
5.	Did either of them have to remain in the hospital for care after the birth?	1 no 2 yes	1 no 2 yes
	If yes, why?	_____	_____

10. Have your twins been diagnosed with any of the following diseases?

	A-child only	B-child only	both	neither
A Hay fever	1	2	3	4
B Allergic rash	1	2	3	4
C Asthma	1	2	3	4
D Recurrent respiratory tract infections (cold, cough, fever)	1	2	3	4
E Recurrent ear infections (more than five during a single year)	1	2	3	4
F Fever seizures	1	2	3	4
G Diabetes	1	2	3	4
H Cross-eyed	1	2	3	4

APPENDIX III

Questions furnishing data for the thesis in the MOTHER'S QUESTIONNAIRE
(Numbers relate to the questions in the original FinnTwin16 baseline questionnaire)

1 When and where were you born?

day___month___ year___ place

3 Do you have children aged 0-6 in your household at this time?

1 no
2 yes, how many?_____

4 Do you have school children (7-16) in your household at this time?

1 no
2 yes, how many? _____ (the twins included)

5 Do you have other children?

1 no
2 yes, how many? _____

13 Have you ever been told by a doctor that you have or have had? (circle also if you answer no)

	no	yes
allergic rhinitis, i.e.,. hay fever	1	2
allergic rash, dermatitis	1	2
asthma	1	2
diabetes	1	2
high blood pressure	1	2
coronary disease (heart infarct or angina pectoris)	1	2
any other long or serious illness (explain)	1	2

SMOKING HABITS

29 Have you in your entire life smoked more than 5-10 packs of cigarettes?

1 No - skip to question 33.
2 Yes

30 Do you smoke or have you at some time smoked cigarettes regularly, in other words daily or almost daily?

1 No - skip to question 33
2 Yes

31 How old were you when you began to smoke cigarettes regularly?
_____ years old

32 Do you still smoke cigarettes regularly?

1 No
How old were you when you stopped smoking? _____ years old
How many did you smoke on average per day before you stopped?
1 none
2 fewer than 5 cigarettes
3 5 - 9 cigarettes
4 10 - 14 cigarettes
5 15 - 19 cigarettes
6 20 - 24 cigarettes
7 25 - 39 cigarettes
8 more than 40 cigarettes

2 Yes

How many cigarettes do you smoke daily on average?

1 none
2 fewer than 5 cigarettes
3 5 - 9 cigarettes
4 10 - 14 cigarettes
5 15 - 19 cigarettes
6 20 - 24 cigarettes
7 25 - 39 cigarettes
8 more than 40 cigarettes

35 What is your occupation, or if you are not working, your previous occupation? (Describe as accurately as possible).

occupation: _____ description: _____

76 Did anyone smoke indoors in your home when the twins were 0-6 years old?

1 No
2 Yes