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THE "SIBLING EFFECT" IN CHILDREN AT HIGH RISK FOR ATOPIC DISORDERS

By

Mircea Calin Botezan

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ABSTRACT

THE "SIBLING EFFECT" IN CHILDREN AT HIGH RISK FOR ATOPIC DISORDERS

By

Mircea Calin Botezan

Several studies have found a strong and consistent inverse relationship between the number of siblings a child has and the likelihood of developing allergic disease: the so called "sibling effect". It was hypothesized that the surrogate variable "number of siblings" reflects the opportunity of having more infections early in childhood, and that allergic sensitization can be prevented by infections acquired during early childhood. This hypothesis is supported by studies that found lower prevalence of sensitization in children from lower SES groups and children from small families who entered early communal day care, and a study conducted in Guinea-Bissau found that measles infection was associated with a large reduction in skin-prick test (SPT) positivity to house dust mite (HDM). The presence of the "sibling effect" was investigated in a preexisting data set, and the following hypotheses were tested:

1. The incidence of sensitization to mite allergens declines with increasing number of siblings.

2. The incidence and prevalence of atopic manifestations (asthma, wheezing, eczema, hay fever, food allergy) declines with increasing number of siblings.

3. The number of older siblings has a more influential effect on sensitization and atopic manifestations.

The data comes from the Study on Prevention of Allergy in Children in Europe (SPACE), a prospective randomized trial designed to evaluate allergen avoidance as a preventive measure against dust mite sensitization. The study population are children at high risk for developing allergic disease: only children with at least one parent reporting history of allergic disorders were selected, and atopic disease in parents was confirmed by SPT or IgE.

The study included 3 cohorts of children: newborns, toddlers (3-4 years of age) and schoolchildren (6-7 years of age). The inclusion criteria were established so that the children would be at high risk of developing allergic disorders (positive SPT/IgE in at least one parent for newborns and toddlers, positive SPT to any allergen other than HDM for schoolchildren), but with no sensitization to house dust mites (HDM). The data available for this study was collected at 12 months follow-up, and the sample size in each group was n = 696 for newborns, n = 636 for toddlers, and n = 242 for schoolchildren.

To test the above hypotheses, the SAS statistical package was used to analyze the data. Frequency tables were obtained for number of siblings and atopic diseases (hay fever, asthma and eczema), as well as for number of siblings and incidence of SPT reactivity at 1-year follow-up. Using logistic

regression, adjusted odds ratios and 95% confidence intervals were calculated, using the group with no siblings as the referent.

I did not detect a sibling effect in this "at risk" population of children, and therefore could not reject the null for hypotheses 1 to 3. The present work does not support the hypothesis that a large number of siblings is inversely associated with sensitization to mite allergens or atopic manifestations for this population of children at higher risk of developing atopic disorders. The absence of the "sibling effect" in a higher risk population may be explained by a strong genetical predisposition, selection bias, reporting bias and exposure misclassification. The findings of the present study encourage further research in order to explain the phenomenon behind the "sibling effect", which may provide one of the most important clues to the causes and prevention of allergic disorders.

ACKNOWLEDGMENTS

The achievement of this work is due in great part to the help and support of numerous individuals. First, I must thank my thesis advisor, Dr. Karmaus, for providing guidance, reading drafts, and granting moral support in the process of completing this work.

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LIST OF ABBREVIATIONS

HDM ..... House Dust Mite

SPT ..... Skin-Prick Testing

IgE ..... Specific Immunoglobulin E Testing

DPT ..... Dermatophagoides pteronyssinus

DF ..... Dermatophagoides farinae

SPACE ..... Study on Prevention of Allergy in Children in Europe

ISAAC ..... The International Study on Asthma and Allergies in Childhood

INTRODUCTION

Atopy is characterized by an abnormal immune response to common antigens, harmless for non-atopic individuals, and it can manifest clinically as asthma, hay fever, atopic eczema, or food allergy. The marked increase in the prevalence of childhood allergic disorders in United States and Western Europe over the past decades is largely unexplained, but it is likely to be attributable to a rise in the prevalence of atopy. This trend is probably not determined by variations in outdoor pollution, but by some unknown factors related to the "Western Lifestyle"(von Mutius et al. 1992), since Eastern Europe did not experience the same rise in prevalence of atopic disorders. Changes in nutritional habits, vaccination schedules, housing characteristics, sanitation practices, hygienic standards, educational models, are all characteristics of westernization and are related to each other, and it's very difficult to discriminate which factor plays a role in the etiology of atopies.

More information on this point came from data suggesting that family size may play a role in the development of atopy. In a British cohort study, Strachan (Strachan 1989) observed that the risk of developing hay fever was inversely related to the individual's number of siblings. More recently, the relevance of family size on atopy and atopic diseases have been confirmed in many other studies conducted especially in Europe, and it is almost certain that the number of siblings in a family is an imprecise surrogate measure for some more influential exposure. If this is the case, the effect of this unknown factor must be

substantial and it may provide the most important clue to the causes and prevention of allergic disorders that has emerged from epidemiological studies over the last decade.

Some studies also found that the number of older siblings may have a stronger protective effect than number of younger siblings, so birth order (number of older siblings + 1) may also play a role in the etiology of atopy. Moreover, two studies found a stronger effect for number of male siblings than for number of female siblings (Strachan et al. 1997a, Svanes et al. 1999), suggesting that gender of siblings may also play a role.

This paper presents the results of an epidemiological study using a preexisting data set of children at higher risk of developing an atopic disease, with the following hypotheses:

1. The incidence of sensitization to mite allergens declines with increasing number of siblings.
2. The incidence and prevalence of atopic manifestations (asthma, wheezing, eczema, hay fever, food allergy) declines with increasing number of siblings.
3. The number of older siblings has a more influential effect on sensitization and atopic manifestations.

Because the data set used did not have the gender of the siblings, I was not able to test if male siblings have a stronger effect than female siblings.

Chapter 1

ATOPY AND ATOPIC DISEASE

Allergy is a specific, acquired change in host reactivity mediated by an immunologic mechanism and causing an untoward physiologic response. Atopy designates an allergic reaction that implies a hereditary factor, and the atopic individual has a predisposition to selective synthesis of IgE antibodies to common environmental antigens. Atopic individuals may differ from nonatopic individuals in their ability to regulate production of IgE antibody or to eliminate allergens that come in contact with mucosal surfaces. They may also fail to control the release or generation of inflammation mediators, or have impaired mediator inactivation process.

The formation of IgE antibodies is revealed in atopic persons by wheal reactions on skin testing with allergen extracts. The capacity to form IgE antibody is also common for nonatopic individuals: under intense allergen exposure or in response to certain allergens such as ascaris, nonatopic individuals may form large quantities of allergen-specific IgE antibodies. But atopic individuals form IgE antibodies on exposure to common environmental antigens such as pollens and house dust, and this distinguishes them from the nonatopic. The most common manifestations of atopy are asthma, allergic rhinitis or hay fever, atopic dermatitis or eczema, and adverse reaction to foods or food allergies (Behrman

et al. 1996). Following is a description of atopic manifestations in the order of their occurrence in childhood.

Adverse reaction to foods or food allergies

Adverse reaction to foods may be caused not only be allergies, but also by enzyme deficiencies and nonimmunologic reactions to tyramine, nitrites, and monosodium glutamate. Individuals with IgE-mediated food reactions consistently show positive skin tests to the suspected food. IgE mediated reactions are characteristically rapid in onset and may present as angioedema of the lips, mouth, uvula, or glottis; as generalized urticaria; as asthma; or occasionally as shock. In such cases, the patient usually recognizes that the symptoms have followed ingestion of a certain food. Persons with such IgE-mediated food allergy are at constant risk of exposure to the offending food hidden in a food mixture (Behrman et al. 1996).

Atopic dermatitis or eczema

Atopic dermatitis is an inflammatory skin disorder characterized by erythema, edema, intense pruritus, exudation, crusting, and scaling. The disease most often begin in infancy and there is a tendency to remission at 3-5 years of age. The earliest lesions are erythematous, weepy patches on the cheeks, with subsequent extension to the remainder of the face, neck, wrists, hands, abdomen, and extensor aspects of the extremities. Involvement of flexural areas characteristically appears later but may occur as popliteal and antecubital dermatitis in early life. Pruritus is marked, the affected infant makes incessant efforts to scratch by rubbing the face on bedclothes and against the sides of the

crib. This trauma to the skin may lead to weeping and crusting, and secondary infection is common and may be extensive (Behrman et al. 1996).

Asthma

Asthma is a leading cause of chronic illness in childhood and it is the most frequent admitting diagnosis in children's hospitals. There is no universally accepted definition of asthma, but it may be regarded as a diffuse, obstructive lung disease with hyper-reactivity of the airways to a variety of stimuli and a high degree of reversibility of the obstructive process, which may occur either spontaneously or as a result of treatment. Also known as reactive airway disease, the asthma complex includes wheezy bronchitis, viral-associated wheezing and atopic related asthma. In addition to bronchoconstriction, inflammation is also a pathophysiologic factor that involves eosinophils, monocytes, and immune mediators.

The signs and symptoms of asthma include cough, which sounds tight and is nonproductive early in the course of an attack; wheezing, tachypnea and dyspnea with prolonged expiration and use of accessory muscles of respiration; cyanosis; hyperinflation of the chest; tachycardia and pulsus paradoxus. Cough may be present without wheezing, or wheezing may be present without cough. Manifestations will vary depending on the severity of the exacerbation, e.g. shortness of breath may be so severe that the child has difficulty walking or even talking. During severe airway obstruction respiratory effort may be great, and the child may sweat profusely (Behrman et al. 1996).

Allergic rhinitis or hay fever

Allergic rhinitis can be classified in two categories: (1) seasonal allergic rhinitis describes a symptom complex seen in children who have become sensitized to wind-borne pollens of trees, grasses, and weeds; (2) perennial allergic rhinitis, when the patient has symptoms all year round, and the causative agents are generally allergens to which the patient is exposed more or less continually: house dust, feathers, allergens or dander of household pets, and mold spores.

The symptoms of allergic rhinitis include sneezing, which is frequently paroxysmal; rhinorrhea, which is often watery and profuse; nasal obstruction; and itching of the nose, palate, pharynx, and ears. Itching, redness, and tearing of the eyes may also occur, causing severe discomfort (Behrman et al. 1996).

Diagnosis: Skin prick test and specific IgE determination

Diagnosis of allergic disorders starts with questions about the symptoms, the allergic history of the patient, and exposure to potential allergens. Physical examination and lung function tests are also useful tools in diagnosing atopic respiratory disorders, but the most objective methods in determining an allergic sensitization remain the skin prick test (SPT) and the specific Immunoglobulin E measurements.

SPT, or the direct skin testing of the patient is an important tool in the diagnosis of IgE-mediated sensitivity. A small quantity of allergen extract is introduced into the skin by prick/puncture (epidermal or epicutaneous method) or by intradermal technique. If the patient's mast cells (cells involved in

inflammatory responses) have IgE antibodies specific for the allergen on their surfaces, an allergen-IgE interaction triggers biochemical events that culminate in release of histamine and other mediators from the mast cell. The histamine acts upon histamine receptors in small vessels, causing increased permeability, dilatation, and axon reflex stimulation, which cause a wheal and flare reaction (Behrman et al. 1996).

Testing for IgE antibodies may be preferable to skin testing in certain groups of patients such as infants, patients with dermatographism or widespread dermatitis, or patients under certain mediation. The most commonly used assays include the radioallergosorbent test (RAST), and various modifications of this test such as Pharmacia CAP, which uses different solid phases to bind allergens and antibody tracers. It has been shown that there is a good correlation between the two methods of testing for sensitization, and that SPT and IgE results appear equivalent (Schuetze et al. 1999).

Chapter 2

A REVIEW OF THE SIBLING EFFECT ON SENSITIZATION AND ATOPIES

One of the strongest and most consistent risk factors for allergy in both children and adults relates to sibship size. This phenomenon, described in the literature as the "sibling effect", was first described by Golding and Peters in a cross sectional analysis of a national cohort known as the British Birth Survey (Golding & Peters 1986). The study was aimed to assess health and behavior in 5-year-old children in Great Britain, as well as epidemiological associations with risk factors such as household conditions, social class, smoking, etc., and attempted to contact the whole population born in one week of 1970 (n=16,567) at around their 5th birthday. Outcomes were measured by asking the mother if the child had ever had asthma, wheezing, eczema or hay fever, and the prevalence was compared for groups with different risk factors. For asthma or wheezing there was no association with the number of other children in the family, but for eczema and hay fever a significant decrease in risk with increasing number of siblings was detected. This association was later found consistently in many other studies not only for eczema and hay fever, but also for asthma, wheezing, and sensitization to allergens measured either by skin prick test (SPT) or by specific blood IgE (IgE).

Review Methods

The review started with a preexisting reference library on the subject, completed with a systemic Medline search for articles that reported their results

on atopic disorders by number of siblings (key words: asthma, hay fever, eczema, atopic dermatitis, atopy, siblings, family size). In most articles, the results section provided adjusted or unadjusted odds ratios for having one of the atopic manifestations (asthma, hay fever, eczema or sensitization measured by SPT or IgE) when having 3 or more siblings vs. no siblings, but some reported their odds ratios for 4 or more siblings vs. none, 2 or more vs. none, and 5 or more siblings vs. no siblings. When only the prevalence for each strata was provided in tables, the unadjusted odds ratio for 3 or more siblings vs. no sibling was calculated, along with the corresponding 95% confidence intervals. A total of 37 articles dealing with atopic disorders and/or sensitization and family size were found, and the associations were summarized in Figures 1 to 4 which show the odds ratios and 95% CI for each atopic disorder and for sensitization; when a study could not be included in the figures because the outcome did not fit in one of the four categories (hay fever, asthma, eczema or sensitization) or the odds ratios were not reported and could not be calculated, the results were summarized in a separate table (Taylor et al. 1983, Bråbäck et al. 1995, Burr et al. 1997, Strachan et al. 1997a, Mattes et al. 1998, Tariq et al. 1998)(Table 1).

Number of siblings and hay fever

One of the most consistent associations between family size and an atopic disorder is the inverse association between the number of siblings and hay fever. All of the 11 studies that report a result on hay fever in relation with family size found a significant negative relationship, with odds ratios between 0.20 and 0.64 for 3 or more siblings versus no siblings (Golding & Peters 1986,

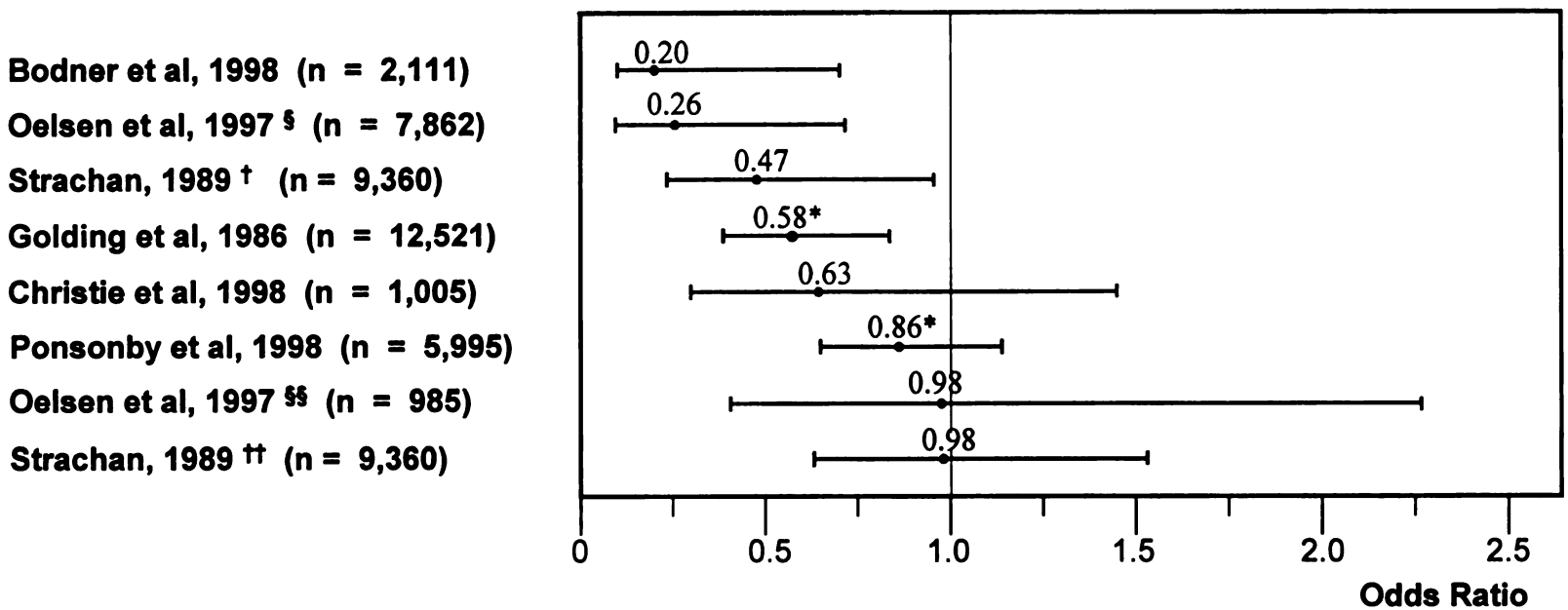

Figure 1. Eczema and number of siblings: 3 or more vs. none

Odds ratios and 95% confidence intervals for large number of siblings and eczema in different studies. Odds ratios are adjusted for other risk factors, except for those marked with an asterisk .

§ specialist diagnosis of atopic dermatitis, older siblings only §§ parent's report of diagnosis of atopic dematitis, older siblings only † older siblings only †† younger siblings only

Strachan 1995, Strachan et al. 1996, Jarvis et al. 1997, Räsänen et al. 1997, Bodner et al. 1998, Bråbäck & Hedberg 1998, Christie et al. 1998, Lewis & Britton 1998, Ponsonby et al. 1998, Leadbitter et al. 1999) (Figure 1). Some of the studies reported the results separately for older and younger siblings (Strachan 1995, Strachan et al. 1996), and when this was the case the effect of older siblings was stronger than the effect of younger siblings. The outcomes measured were history of hay fever, current hay fever, hay fever in the past 12-months, and doctor's diagnosis of hay fever; the age when outcomes were measured varied between 7 and 44 years.

Number of siblings and asthma or wheezing

Although the negative association between asthma or wheezing and family size is less consistent, from 20 studies who reported their results on asthma or wheezing in relation to the number of siblings, 14 studies found a negative association with odds ratios ranging from 0.30 to 0.84 (Crane et al. 1994, Shaw et al. 1994, Stoddard & Miller 1995, Jarvis et al. 1997, Rona et al. 1997, Sunyer et al. 1997, Christie et al. 1998, Ponsonby et al. 1998, Leadbitter et al. 1999, Rona et al. 1999, Wickens et al. 1999, Xu et al. 1999), and in 10 of those the relationship was statistically significant; 4 studies found no association to family size (Räsänen et al. 1997, Bodner et al. 1998, Bråbäck & Hedberg 1998, Rona et al. 1999), and only 2 studies found a positive association of family size to asthma or wheezing (Davis & Bulpitt 1981, Weitzman et al. 1990) (Figure 2). The results were reported for the following outcomes: ever wheezing or

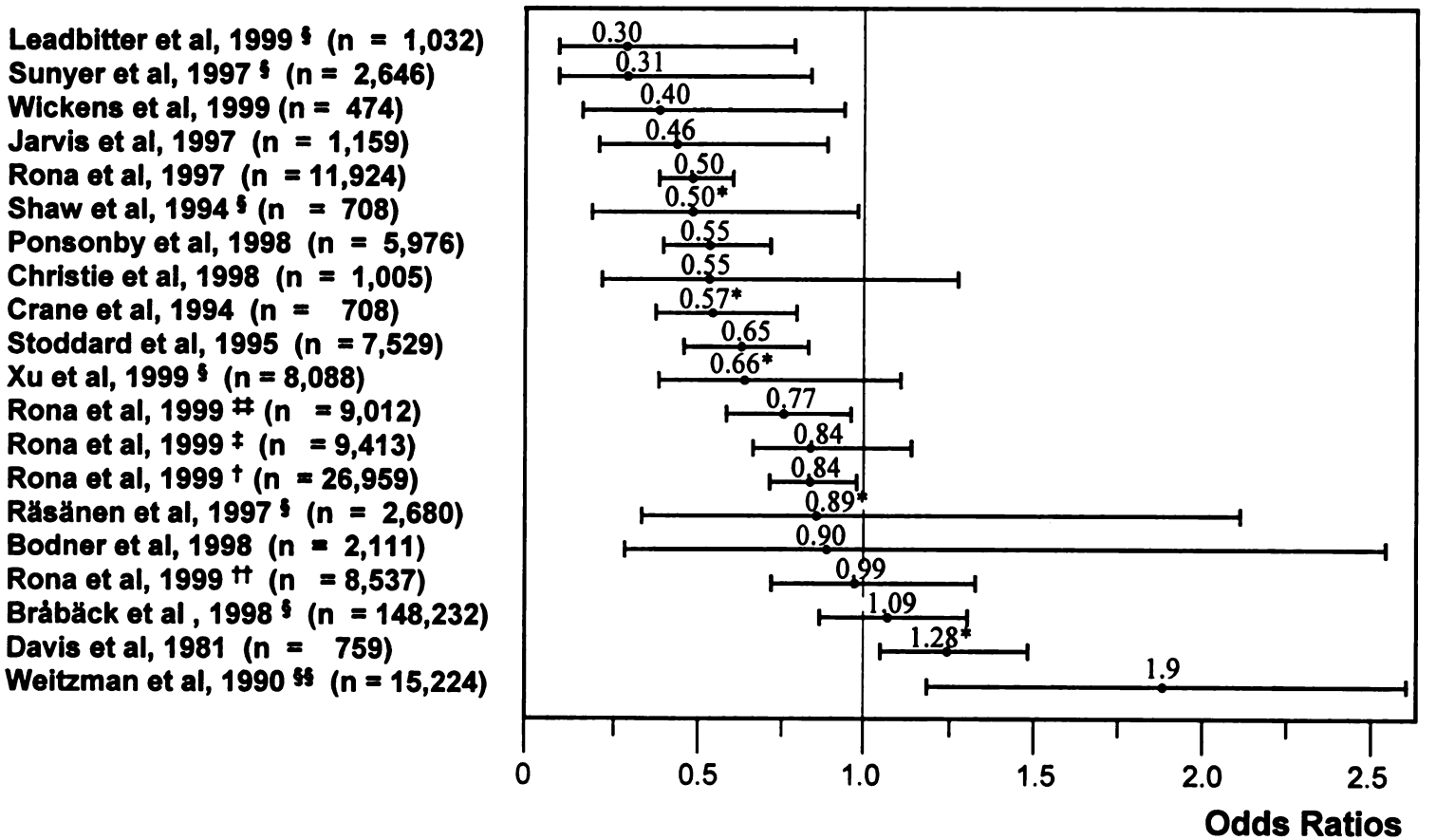

Figure 2. Asthma or wheezing and number of siblings: 3 or more vs. none

Odds ratios and 95% confidence intervals for large number of siblings and asthma or wheezing in different studies. Odds ratios are adjusted for other risk factors, except for those marked with an asterisk .

§ older siblings only §§ large family size (>5 members) † all surveys †† 1977 survey ‡ 1986 survey ‡‡ 1994 survey

whistling in the chest or in the past 12 months, ever asthma or asthma in the past 12 months, doctor's diagnosis of asthma. One of the articles reports the results of three surveys with same questions on respiratory symptoms at three different times: 1977,1986, and 1994 (Rona et al. 1999). Each survey included schoolchildren aged 5 to 11 from the same geographical area in the United Kingdom, and although there is a significant negative association of asthma with family size when data from all surveys is pooled together, the results show that the odds ratios of asthma or wheeze by family size changed over time. In the 1977 survey there was no association, in 1986 there is a non-significant weak association, while in the 1994 survey the association becomes stronger and statistically significant, suggesting that the sibling effect for asthma and wheezing may be either stronger for more recent cohorts or easier to detect due to recently increased prevalence.

Eczema and number of siblings

Only seven of the reviewed studies reported results on eczema and family size, and all found an negative association with family size or no association at all: 5 reported an inverse association with number of siblings (Golding & Peters 1986, Olesen et al. 1997, Bodner et al. 1998, Christie et al. 1998, Ponsonby et al. 1998), of which 3 were statistically significant, one found an significant inverse association for older siblings only, while for younger siblings there was no association (Strachan 1989), and one study reported no association between eczema and family size (Olesen et al. 1997) (Figure 3). The outcomes measured

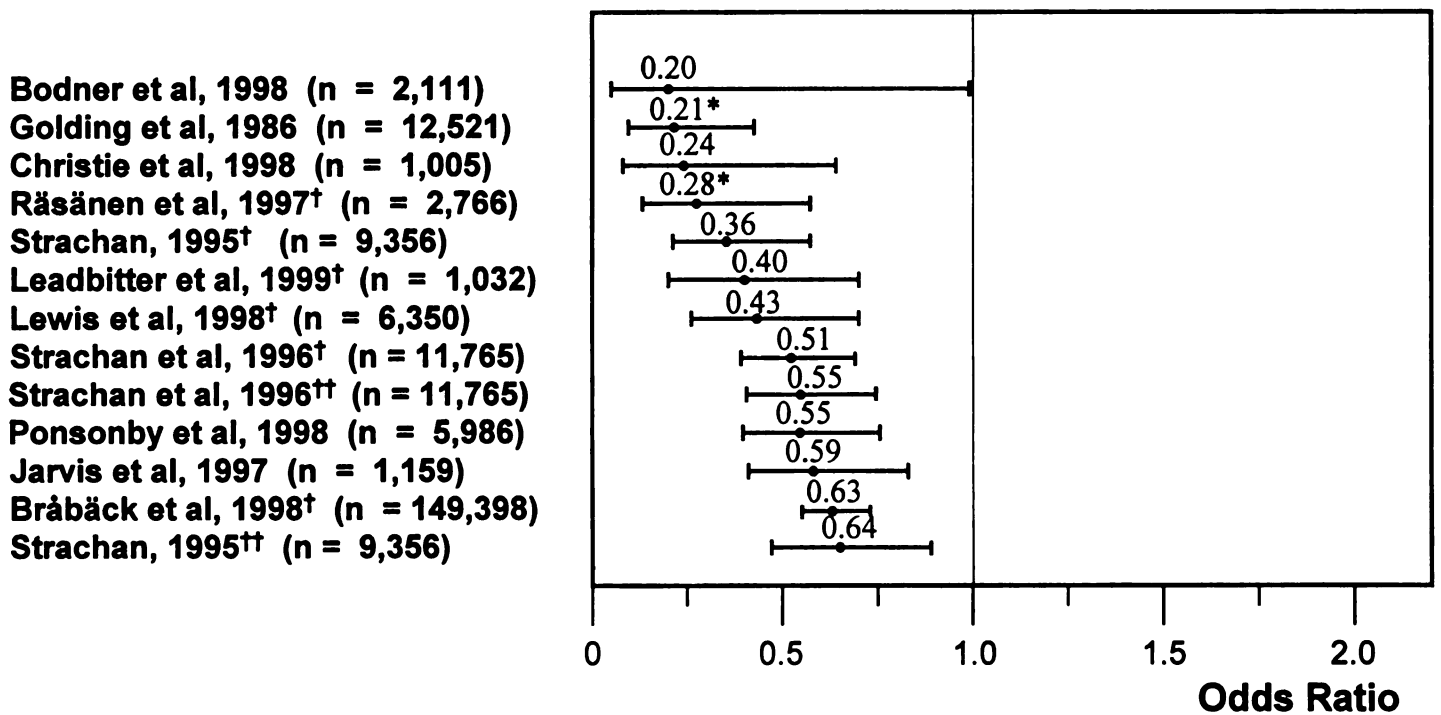

Figure 3. Hay fever and number of siblings: 3 or more vs. none

Odds ratios and 95% confidence intervals for large number of siblings and hay fever in different studies. Odds ratios are adjusted for other risk factors, except for those marked with an asterisk.

† older siblings only †† younger siblings only

were history of eczema, eczema in the first year of life, parental report of doctor's diagnosis of eczema, and specialist diagnosis of atopic dermatitis.

SPT / IgE reactivity and number of siblings

Sensitization to specific allergens is also consistently found to be negatively associated with family size. In all of the reviewed studies sensitization was defined as a positive skin prick test (SPT) reaction or a positive specific immunoglobulin E (IgE) serum antibody to any of the allergens tested. From 12 studies reporting results on sensitization in relation to family size, 11 found an inverse association of sensitization with increasing number of siblings (Davis & Bulpitt 1981, von Mutius et al. 1994, Nowak et al. 1996, Strachan et al. 1996, Forastiere et al. 1997, Jarvis et al. 1997, Matricardi et al. 1997, Strachan et al. 1997b, Matricardi et al. 1998, Storm van's Gravensande et al. 1998, Leadbitter et al. 1999, Svanes et al. 1999), of which 6 were statistically significant, and only one study found a positive association, which was unadjusted for possible confounders (Davis & Bulpitt 1981) (Figure 4). Three of the 11 studies who showed a negative relationship had their results reported separately for younger and older siblings, and although both younger and older siblings seemed to protect against sensitization, in two of the three studies the association was significant only for older siblings, and all showed a stronger effect for older siblings.

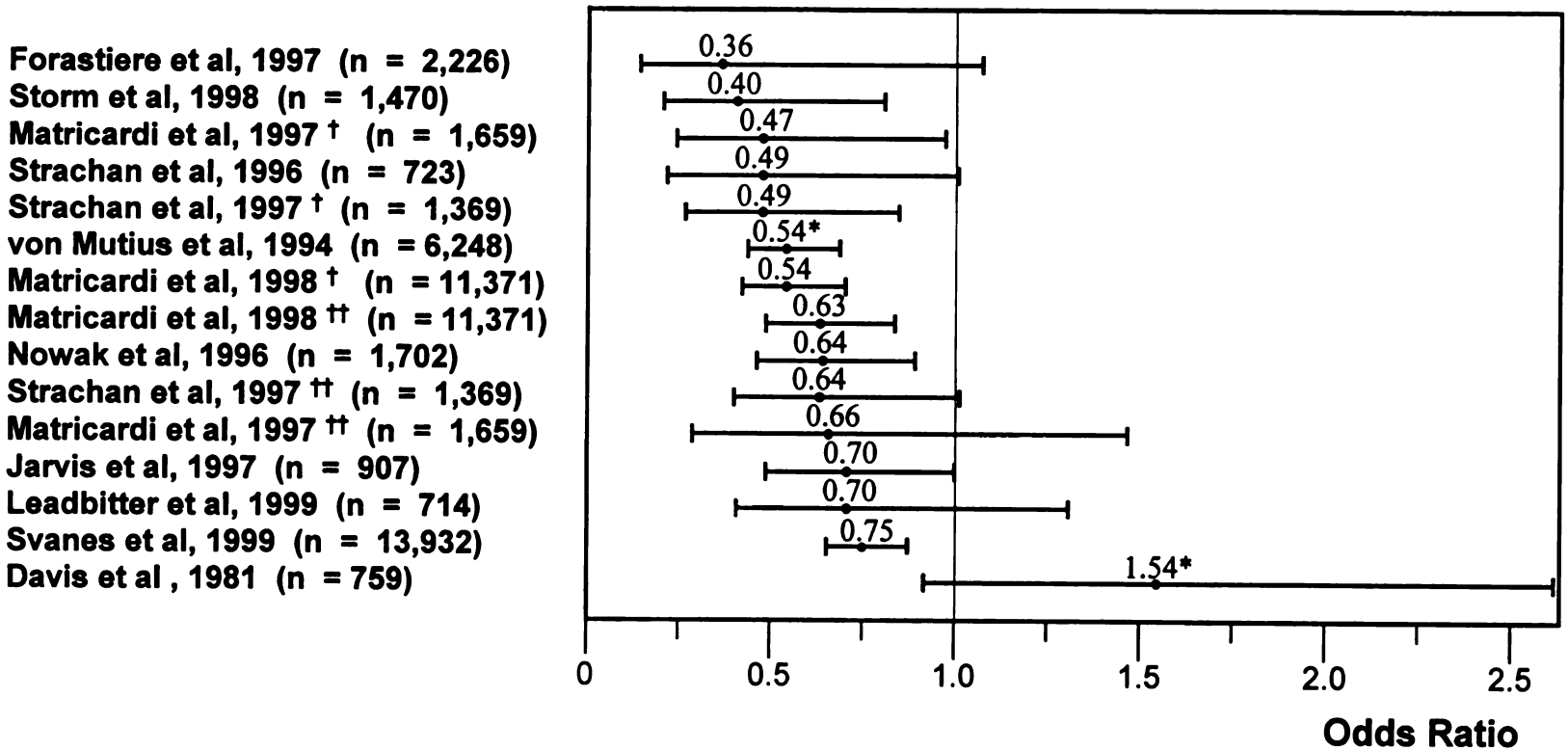

Figure 4. SPT/IgE reactivity and number of siblings: 3 or more vs. none

Odds ratios and 95% confidence intervals for large number of siblings and SPT or IgE reactivity to at least one allergen in different studies. Odds ratios are adjusted for other risk factors, except for those marked with an asterisk.
† older siblings only †† younger siblings only

Review Summary

The "sibling effect", defined as the inverse association between a large number of siblings and atopy, was first described for a British national cohort in 1986 (Golding & Peters 1986), and was later consistently reported by a number of studies from different parts of the world, mostly Europe. From 37 studies reviewed, 27 found a negative association between number of siblings and all of the outcomes studied, 8 found an inverse association only for some of their outcomes, and only 2 reported a positive relationship. The effect is more consistent for hay fever and sensitization than for asthma or wheezing and eczema, probably because hay fever has specific symptoms and it's less likely to be misdiagnosed, and sensitization is measured by standard procedures. Asthma is more difficult to diagnose in a consistent manner since wheezing, its most important symptom, can also be associated with respiratory infections, inhalation of cold air and physical effort. This might explain why some studies found a sibling effect for hay fever but failed to find the same effect for asthma (Räsänen et al. 1997, Bråbäck & Hedberg 1998, Christie et al. 1998).

Although the magnitude and consistency of the sibling effect are remarkable, the process behind this association is largely unknown. Further research is needed to investigate the factors acting between a large family size and protection against atopic disorders, with possible applications in public health and prevention.

Table 1. Studies showing a relationship between family size and atopic disease that could not be included in figures 1 to 4 (no OR reported or outcome did not fit in one of the four categories)

Author and year	Outcome measured	Findings	Measure of association
BRÅBÄCK ET AL, 1995 N = 2,232	SPT	The number of siblings and domestic crowding were inversely related to sensitization	OR = 0.58 (0.43, 0.77) for number of persons per room
BURR ET AL, 1997 N = 437 for SPT N = 338 for IgE	SPT, IgE, wheezing, eczema, hay fever (children with family history of atopy)	There was a non-significant negative association of SPT and IgE with number of older siblings	p = 0.13 for SPT p = 0.12 for IgE
MATTES ET AL, 1998 N = 3,165	Atopic disorder (asthma, hay fever or eczema)	Inverse relationship between number of older siblings and atopic disease	OR = 0.4 (0.19, 0.83) for +3 older siblings OR = 1.14 (0.70, 1.85) for +3 younger siblings
STRACHAN ET AL, 1997 N = 11,042	Inhalant allergy (cat, pollen, or dust) and non-inhalant allergy (insect bites or something else)	Inhalant allergy was inversely related with the number of siblings	OR = 0.76 (0.59, 0.97) (not adjusted)
TARIQ ET AL, 1998 N = 1,215 for atopic ilness N = 981 for SPT	Atopic disorder (asthma, eczema or hay fever) SPT	Weak inverse relation of number of siblings with atopic illness and SPT	PR = 0.41 for atopic illness (not significant) PR = 0.61 for SPT (not significant), 4 siblings vs. no siblings
TAYLOR ET AL, 1983 N = 12,743	Eczema, hay fever, wheezing and asthma	Having older siblings was inversely associated with hay fever, no associations with eczema of asthma	PR = 0.56 of having older siblings vs. no older siblings for hay fever (no CI or p value provided)

Chapter 3

THE SPACE STUDY

For this project I used a preexisting data that was collected for the Study on Prevention of Allergy in Children in Europe (SPACE). The SPACE Project is a 3-year multicenter study involving Germany, Austria, Greece, Lithuania and England. The study aimed to assess the effectiveness of the use of House Dust Mite (HDM) allergen impermeable mattress covers combined with health education from health professionals (intervention arm), in reducing sensitization to airborne allergens and the development of atopic symptoms, such as asthma, eczema, hay fever, or any combination of these. The focus was on three cohorts of high risk children from parents screened for symptoms and reactions to aeroallergens (see inclusion criteria): Newborns, Toddlers aged 24—48 months, and Schoolchildren aged 4—7 years. The study was designed as a single-blinded intervention: the staff examining the children is blinded and the parents do not know if they belong to the intervention or control arm, but they were aware of having received a mattress cover and might therefore detected themselves as being in the intervention group. The project made use of questionnaires during recruitment to record clinical allergic disorders in the children and their parents. Their atopic status was assessed objectively by skin-prick testing (SPT), and at some centers, by measuring specific immunoglobin E

(IgE). The children were followed-up for 24 months, but only 12-months follow-up data was available for this project.

The inclusion criteria were: Newborns: Positive skin-prick test/IgE in either parent to any one allergen, more than 37 weeks' gestation, and less than 7 days in special care. Toddlers: Positive skin-prick test/IgE in either parent to any one allergen, plus negative test of the child to house-dust mite allergens. Schoolchildren: Negative skin-prick test to house dust mite allergens, but positive skin-prick test to any other aeroallergen.

The cohorts of children were selected to be at higher risk in order to increase the efficiency of the intervention trial, and children were free of sensitization to dust mites at the beginning of the study. The cohort was followed-up for 12 months, when sensitization was tested by SPT or specific IgE measurements, and information about allergic symptoms were collected using standardized questionnaires derived from the International Study on Asthma and Allergies in Childhood (ISAAC). The timeline of the SPACE study from recruitment to the 12-months follow-up is described in Figure 5.

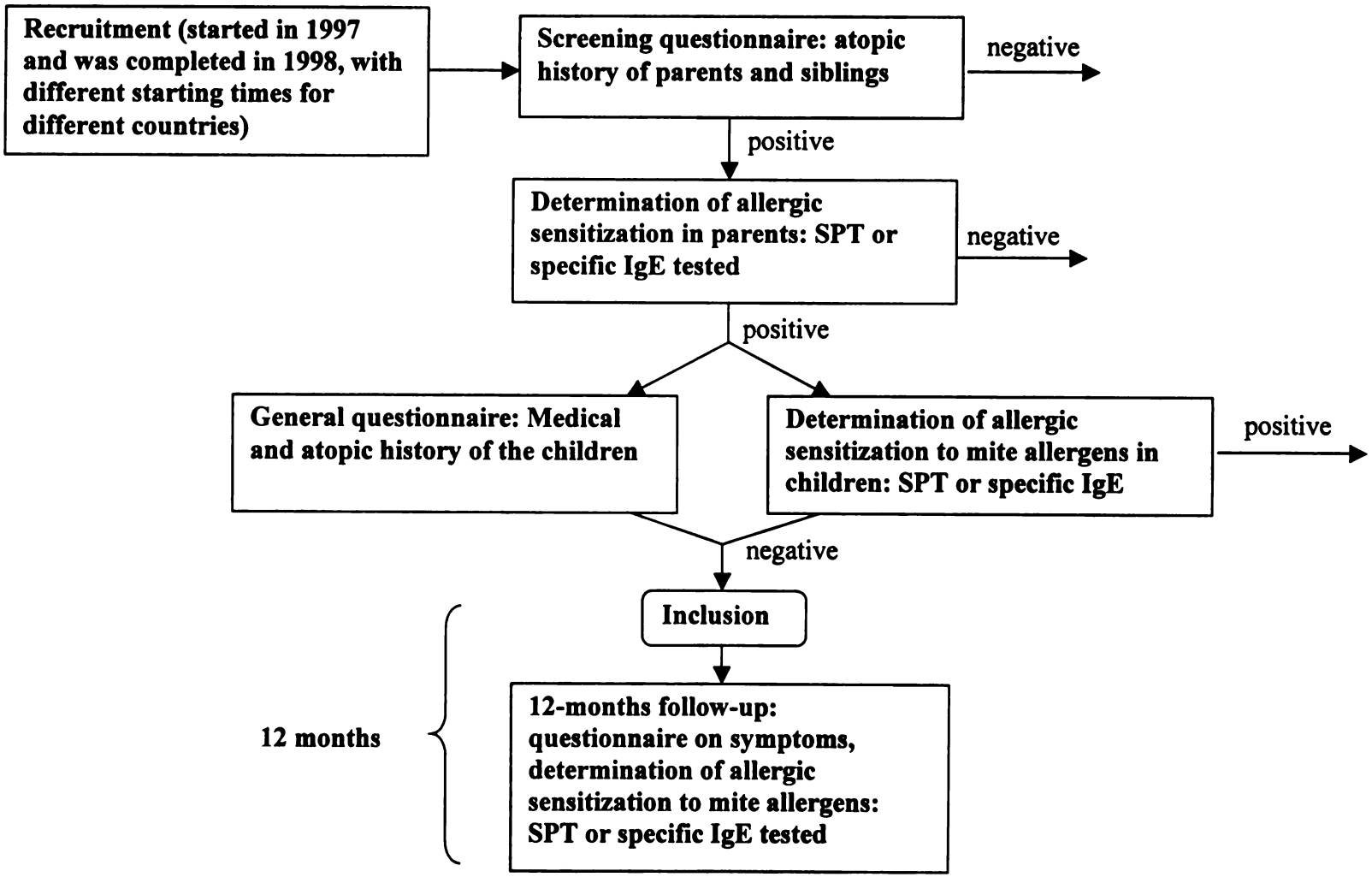

Figure 5. Time-line flow chart of the SPACE study

Chapter 4

METHODS

Population

The recruitment of the study population was carried out over a period of 12 months in 5 European countries: England, Germany, Greece, Lithuania and Austria, using the appropriate way of approaching participants for each country. The recruitment procedure for each cohort (newborns, toddlers and schoolchildren) is described in detail in Figures 6 to 8. After the completion of the recruitment and screening procedure, 1574 children at higher risk of developing atopic disorders were included in the study: 696 newborns, 636 toddlers and 242 schoolchildren. Twelve months after inclusion in the study, 1,371 of these (87.1%) had a skin prick test performed or an IgE measurement to determine sensitization to mite allergens (Dermatophagoides pteronyssinus, DPT or Dermatophagoides farinae, DF), and 1,450 (92.1%) had completed the questionnaire at 12-months follow-up.

Immunologic outcome

To avoid misclassification, only objective and reliable methods such as skin prick testing (SPT) and specific IgE serum antibody measurement were used to assess sensitization. SPT is a simple and low cost method, but in some

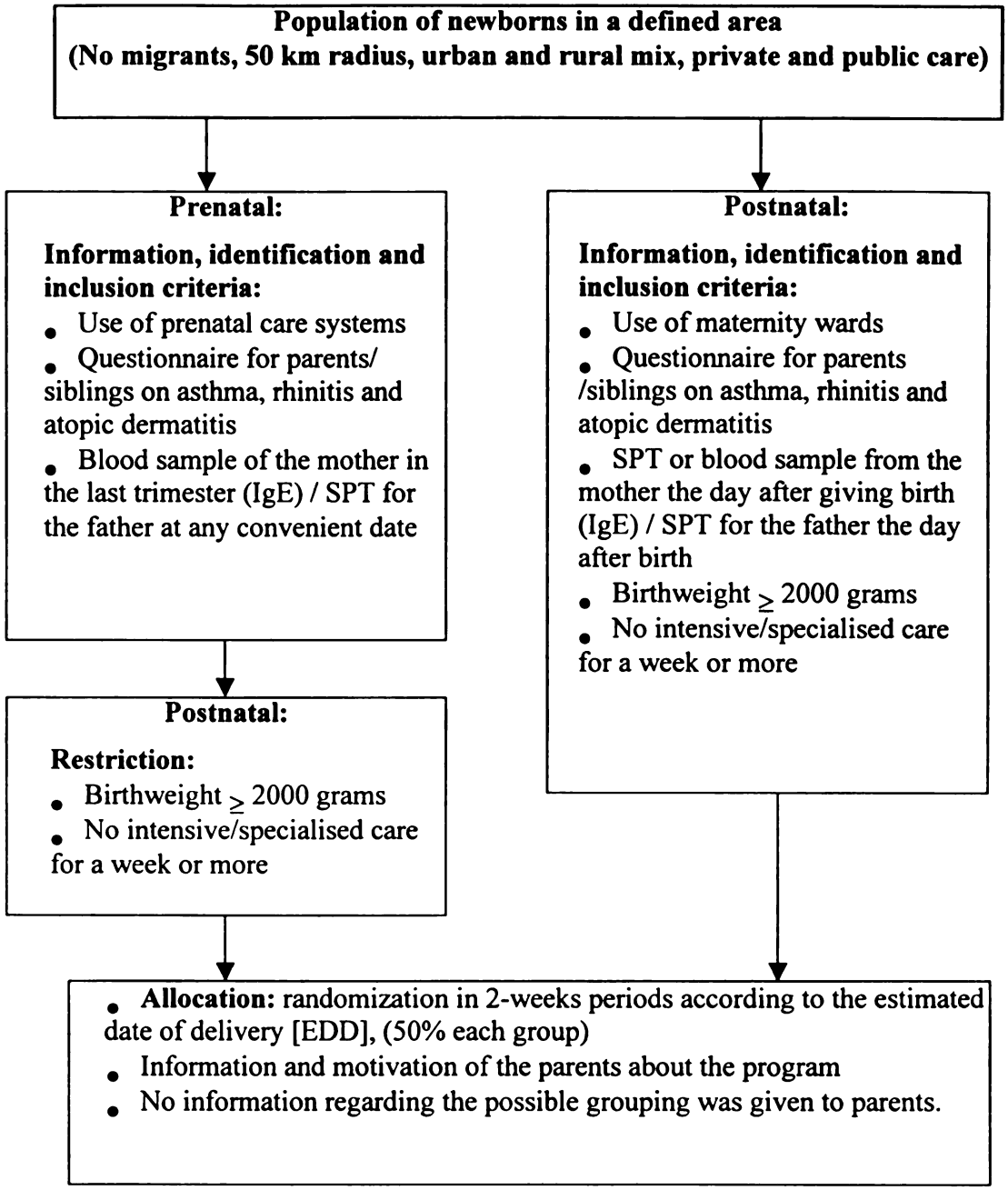

Figure 6. Recruitment of new-borns at higher risk

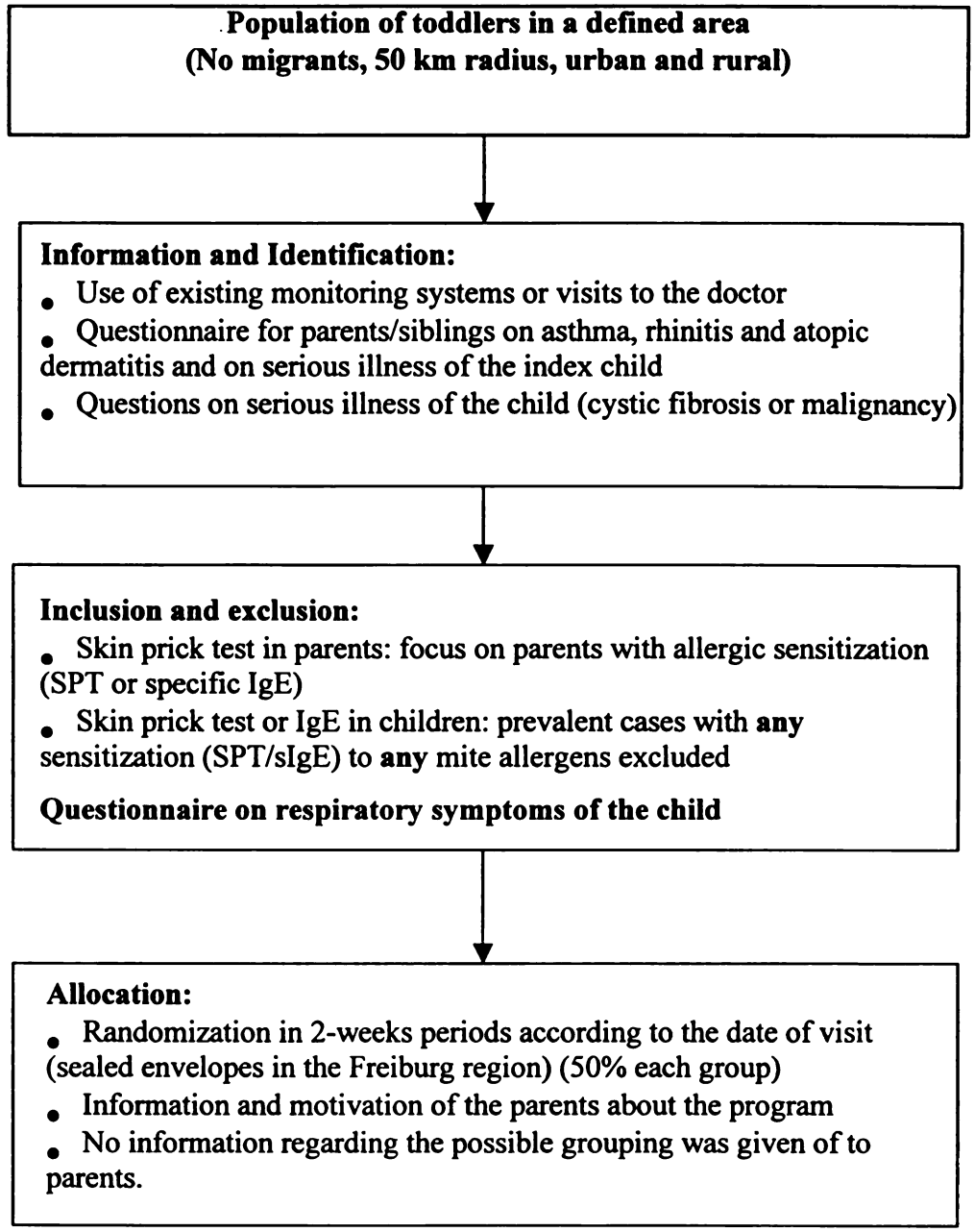

Figure 7. Recruitment of toddlers at higher risk

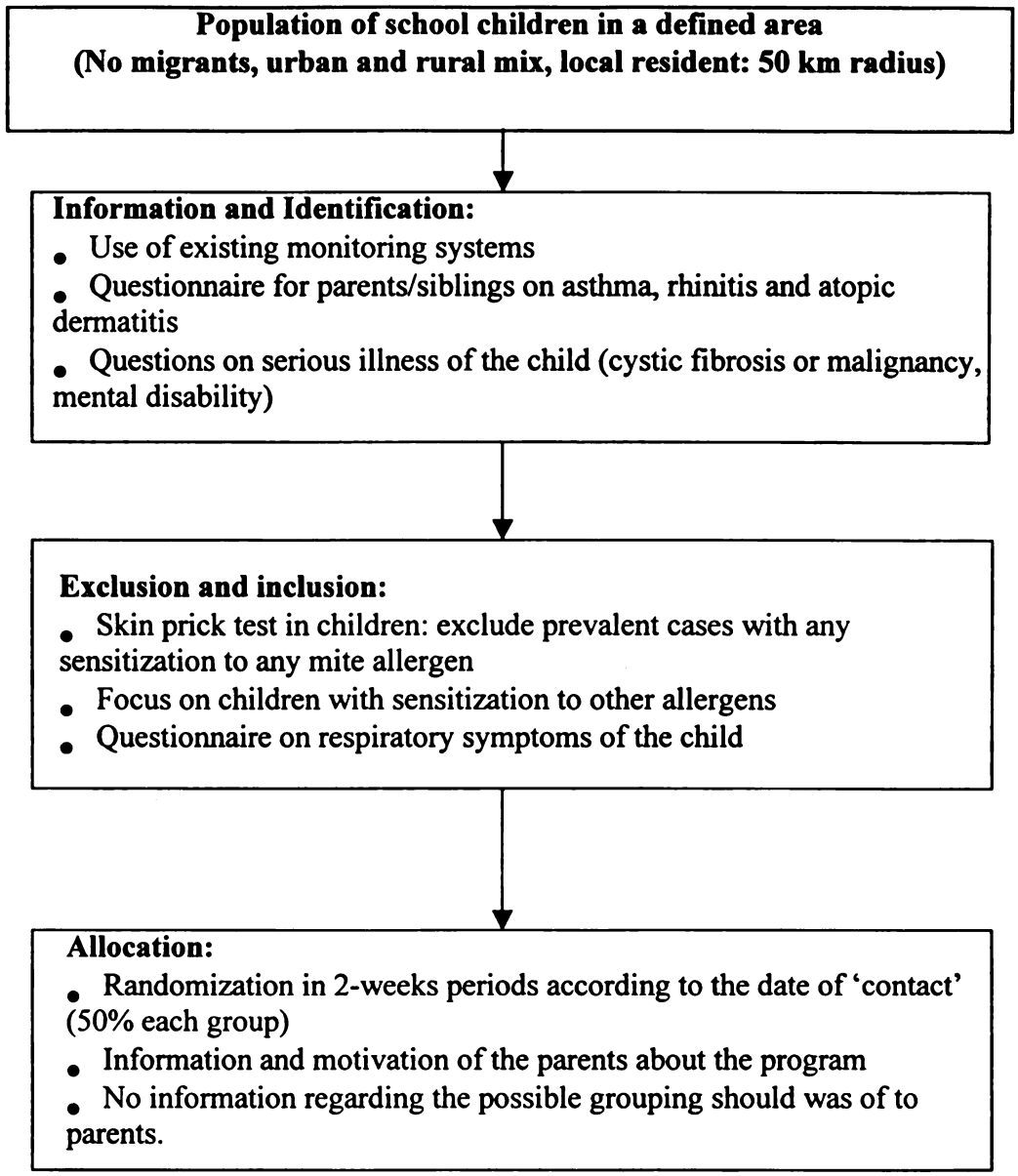

Figure 8. Recruitment of school children at higher risk

countries is not accepted for infants and toddlers. Therefore, IgE was used as an alternative and SPT alone was used only in schoolchildren. For SPT, purified and standardized test extracts from the same source were used in all countries, and testing followed a standardized protocol: a definite sensitization against a certain allergen required a wheal diameter of at least 2 mm for the allergen and a ratio wheal diameter allergen/wheal diameter histamine of at least 0.5; IgE measurements were performed in a central laboratory using the same test system for all samples. The allergens tested routinely in all centers were D. pteronyssinus and D. farinae, and all children positive to mite allergens at 12 months represent incident cases since they were SPT / IgE negative for mite allergens at the beginning of the study.

Questionnaires

To investigate the impact of allergen avoidance with regard to allergic disease, validated questionnaires adapted from the ISAAC study were used to ascertain the child's symptoms when the child was included in the study and at 12-months follow up. The questions were designed to detect the atopic manifestations in children according to the description in chapter one. Before the child was included in the study, at the end of the recruitment procedure, the parents were asked the following questions about the child:

1. Does your child suffer from food allergies?

2. Has your child ever had eczema?

3. Has your child ever had wheezing, or whistling in the chest at any time in the past?

4. Has your child ever had asthma?

5. Has your child ever had hay fever?

The following questions were asked at the 12-months follow-up:

1. "Was a doctor's diagnosis of food allergy made in your child in the last 12 months?" (in the last 6 months for newborns)

2. "Was a doctor's diagnosis of eczema made in your child in the last 12 months?" (in the last 6 months for newborns)

3. "Has your child had wheezing or whistling in the chest in the last 12 months ?"

4. "Has your child ever had asthma?"

5. "Was a doctor's diagnosis of asthma made in your child in the last 12 months?"

6. "Was a doctor's diagnosis of hay fever made in your child in the last 12 months?"

As a result, the following outcomes could be assessed: 1) lifetime prevalence of asthma, using a positive answer to the questions about asthma in either questionnaire; 2) 12 months asthma incidence, by excluding all those who had asthma symptoms when included in the study; 3) lifetime prevalence of wheezing or whistling in the chest, by taking a positive answer from either questionnaire; 4) incidence of doctor's diagnosis of eczema, hay fever, or food allergy, by excluding all those who had the corresponding symptoms at inclusion.

To assess the potential confounding variables, the following questions were asked at the time of recruitment about pet ownership, smoking in the household, smoking during pregnancy, and parent's education:

1. Do you have a pet? If yes, what kind of pet?

2. Have you ever had a pet in this house?

3. How many cigarettes are smoked in your home per day?

4. Did you smoke during this pregnancy? If yes, for how long? How many cigarettes per day?

5. What is the highest education level have completed (mother and father)?

- Left school before compulsory level
- Left school at compulsory level
- Left school between compulsory and high level
- Left school at high level
- Manual education after school
- Theoretical education after school
- University

At the 12-months follow-up, the following questions were asked about potential confounders:

1. Have you obtained a new pet since the beginning of the study?

2. Have you given up a pet since the beginning of the study? (With possible answers "yes", "no", and "never had one")

3. Was your child regularly exposed to pets elsewhere since the beginning of the study?

4. Does anyone in your household smoke?

5. How many cigarettes have been smoked on average in your home daily since the beginning of the study?

6. Was your child exposed to cigarette smoke elsewhere since the beginning of the study?

Statistical analysis

The unadjusted incidence of specific sensitization to dust mite allergens was calculated by number of siblings and number of older siblings. The same was done for lifetime prevalence of asthma, 12-months asthma incidence, lifetime prevalence of wheezing or whistling in the chest, and doctor's diagnosis of eczema, hay fever and food allergy. A logistic regression model was used to assess the independent effect of the number of siblings and number of older siblings on sensitization to mite allergens and symptoms after adjustment for potential confounding variables (age, gender, birthweight, pet ownership, smoking in household, smoking during pregnancy, parents' education, age of the mother when the child was born, and location). From this, the odds ratios and 95 % confidence intervals for the outcome variable was derived, using the group with no siblings (or no older siblings) as the referent group. All statistical analyses were performed using SAS version 8.00.

Chapter 5

RESULTS

A description of the study population is presented in Table 1. Gender distribution was fairly equal between countries and all centers had more males than females, with the exception of Austria. Pet ownership ever or at 12-months follow-up varied considerably between countries and was highest in England (62.8% and 61% respectively) and lowest in Greece (18.1% and 19.1% respectively). There were also variations between countries for smoking in the household (50.1% in Greece, 8.6% in Germany), smoking during pregnancy (18.3% in Austria, 1.7% in Lithuania), mother age at child's birth, and parents education (Table 2). The age distribution by country in illustrated in Table 3 and reflects the different age cohorts included in each country: newborns (England, Germany and Austria), toddlers (England, Germany, Greece and Lithuania), and schoolchildren (England, Greece, and Lithuania).

Tables 4 (page 35) shows the relationships between the number of siblings and incidence of specific sensitization to dust mite for all children and for each age group (newborns, toddlers and schoolchildren). The overall 12-months incidence of sensitization to dust mite allergen was 4,8 % and it was higher for toddlers and schoolchildren (5.6 % in each group) than for newborns (3.8 %). Table 11 shows the incidence of sensitization to mites by older siblings.

Table 2. Description of the population by country (%)

	England n=285	Germany n=232	Greece n=371	Lithuania n=180	Austria n=382
Males	54.0	55.2	54.4	56.7	47.4
Low birthweight	2.5	4.7	4.3	6.7	0.8
Pet ownership ever	62.8	25.9	18.1	35.6	22.3
Pet ownership at follow-up	61.0	26.3	19.1	22.8	36.1
Smoking in the household	22.5	8.6	50.1	25.0	23.3
Smoking during pregnancy	16.8	12.5	16.2	1.7	18.3
Mother age at child's birth					
19 or less	3.2	0.4	0.3	5.6	1.8
19-25	25.3	6.0	15.6	52.8	23.0
26-30	34.4	47.4	41.0	26.7	43.2
31-35	27.7	35.3	32.9	12.2	26.7
36 or more	9.5	10.8	10.2	2.8	5.2
Mother's education					
high (university)	8.8	32.3	43.4	37.8	20.4
medium level	29.1	50.9	43.4	42.2	66.2
normal level	60.3	16.8	13.2	17.8	13.3
Father's education					
high (university)	14.0	40.1	46.9	38.3	25.4
medium level	22.8	20.7	31.3	38.3	20.9
normal level	60.0	38.4	21.3	18.9	53.7
Total	**19.7**	**16.0**	**25.6**	**12.4**	**26.3**

Table 3. Age distribution at 12-months follow-up by country

Age	England n=285	Germany n=232	Greece n=371	Lithuania n=180	Austria n=382	Total N = 1,450
1 year	146	142	3	0	380	671 (46.2%)
2 years	32	15	6	2	2	57 (3.9%)
4 years	56	39	74	24	0	193 (13.3%)
3 years	18	30	156	32	0	236 (16.3%)
5 years	7	6	44	39	0	96 (6.6%)
6 years	11	0	21	12	0	44 (3.0%)
7 years	7	0	28	30	0	65 (4.5%)
+ 8 years	8	0	39	41	0	88 (6.1%)

Lifetime prevalence of asthma was 12.6 % overall (2.2 % for newborns, 18.5 % for toddlers, 28.0 % for schoolchildren), increasing with age as expected (Table 5). Lifetime prevalence of asthma in relation to number of siblings and number of older siblings is shown in Table 5 and Table 12 respectively.

Overall, 12-months asthma incidence was 4.6 % (2.2 % for newborns, 6.9 % for toddlers and 7.2 % for schoolchildren), following the same pattern as lifetime prevalence of asthma (Table 6). 12-months asthma incidence by number of siblings and by number of older siblings is presented in Table 6 and Table 13 respectively.

Lifetime prevalence of wheezing or whistling in the chest was 35.4 % for all children, 22.8 % for newborns, 46.5 % for toddlers, and 45.8 % for schoolchildren (Table 7), and it was higher for toddlers and schoolchildren than for newborns. Prevalence of wheezing or whistling in the chest by number of siblings is shown in Table 7, and by number of older siblings in Table 14.

Incidence of doctor's diagnosis of eczema was 9.8% for newborns (6 months incidence), 5.8 % for toddlers and 2.8% schoolchildren (12-months incidence) (Table 8). If we assume that there is no time trend in eczema incidence for newborns, we could take the double of the 6 months incidence (or 19.2%) in order to compare it to the 12 months incidence of toddlers and schoolchildren. As expected, incidence of eczema is higher in newborns and becomes less of a problem with increasing age (Table 8). Incidence of doctor's diagnosis of eczema by number of siblings and number of older siblings is shown in Table 8 and Table 15 respectively.

Twelve months incidence of doctor's diagnosis of hay fever was 5.9 % for toddlers and schoolchildren only taken together, 3.5 % in toddlers and 13.3 % in schoolchildren (Table 9). Incidence of hay fever also followed an expected pattern, increasing with age. The relationship between incidence of hay fever and number of siblings is illustrated in Table 9, and with number of older siblings in Table 16.

Incidence of doctor's diagnosis of food allergy was 3.3 % for newborns (6 months incidence), 2.7 % for toddlers and 2.8% for schoolchildren (12-months incidence) (Table 10). Again, if we assume no time trend in incidence for newborns, the 12-months incidence would be 6.6% and twice the incidence for toddlers and schoolchildren and thus decreasing with age, as expected. Incidence of food allergy is shown by number of siblings in Table 10 and by number of older siblings in Table 17.

When looking at the above outcomes in relation to number of siblings, I could not detect an inverse association of number of siblings with either sensitization to mite allergens or any symptom recorded in the study's questionnaires. When the analysis was repeated for number of older siblings and/or restricted by group (newborns, toddlers or schoolchildren), the "sibling effect" failed to show up. There were very few significant associations of number of siblings or older siblings with any of the outcomes measured, and when an association was found it was usually against the "sibling effect".

Because the findings might be influenced by the intervention, I restricted the study population to controls only, and the results were not different. I also looked separately at different countries and I could not see a "sibling effect" in any of the study locations.

Table 4. **Sensitisation to dust mites by sibling number: 12-months crude incidence and adjusted odds ratios (aOR)**

Siblings	Newborns N = 622		Toddlers N = 536		Schoolchildren N = 213		All children N = 1,371	
	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)
None	4.3 % (16/368)	1.00 (reference)	7.8 % (11/141)	1.00 (reference)	4.9 % (2/41)	1.00 (reference)	5.3 % (29/550)	1.00 (reference)
1	2.7 % (5/187)	0.50 (0.17, 1.46)	2.9 % (9/305)	0.39 (0.15, 1.00)	3.8 % (5/132)	0.89 (0.16, 4.89)	3.0 % (19/624)	0.58 (0.31, 1.08)
2	2.1 % (1/47)	0.48 (0.06, 3.83)	11.1 % (7/63)	1.67 (0.55, 5.08)	12.1 % (4/33)	3.60 (0.58, 22.48)	8.4 % (12/143)	1.57 (0.74, 3.37)
3 +	10.0 % (2/20)	3.90 (0.67, 22.76)	11.1 % (3/27)	1.11 (0.25, 5.05)	14.3 % (1/7)	4.00 (0.26, 60.40)	11.1% (6/54)	1.95 (0.71, 5.34)
Total	3.8 % (24/622)		5.6 % (30/536)		5.6 % (12/213)		4.8 % (66/1,371)	

Table 5. Lifetime prevalence of asthma by sibling number: crude prevalence and adjusted odds ratios (aOR)

Siblings	Newborns N= 670		Toddlers N = 566		Schoolchildren N = 214		All children N = 1,450	
	Crude Prevalence	aOR (95% CI)	Crude Prevalence	aOR (95% CI)	Crude Prevalence	aOR (95% CI)	Crude Prevalence	aOR (95% CI)
None	1.0 % (4/399)	1.00 (reference)	17.2 % (26/151)	1.00 (reference)	31.7 % (13/41)	1.00 (reference)	7.3 % (43/591)	1.00 (reference)
1	0.0 % (4/200)	2.01 (0.49, 8.23)	20.4 % (66/323)	1.11 (0.64, 1.91)	29.3 % (39/133)	0.57 (0.23, 1.41)	16.6 % (109/656)	1.32 (0.86, 2.00)
2	7.8 % (4/51)	7.83 (1.85, 33.19)	14.1 % (6/94)	0.68 (0.28, 1.61)	15.1 % (5/33)	0.23 (0.06, 0.93)	12.2 % (18/148)	0.83 (0.44, 1.57)
3 +	15.0 % (3/20)	16.35 (2.76, 96.73)	25.0 % (7/28)	0.98 (0.35, 2.78)	42.9 % (3/7)	0.69 (0.10, 4.83)	23.6 % (13/55)	1.78 (0.83, 3.81)
Total	2.2 % (15/670)		18.5 % (105/566)		28.0 % (60/214)		12.6 % (183/1,450)	

Table 6. 12 months asthma incidence by sibling number: crude incidence and adjusted odds ratios (aOR)

Siblings	Newborns N= 670		Toddlers N = 492		Schoolchildren N = 166		All children N = 1,328	
	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)
None	1.0 % (4/399)	1.00 (reference)	6.0 % (8/133)	1.00 (reference)	9.7 % (3/31)	1.00 (reference)	2.7% (15/563)	1.00 (reference)
1	0.0 % (4/200)	2.05 (0.50, 8.37)	8.2 % (23/280)	1.36 (0.56, 3.31)	6.9 % (7/101)	0.33 (0.06, 1.86)	5.8 % (34/581)	1.51 (0.77, 2.96)
2	7.8 % (4/51)	7.95 (1.87, 33.73)	3.5 % (2/57)	0.55 (0.11, 2.82)	6.7 % (2/30)	0.40 (0.04, 4.33)	5.8 % (8/138)	1.49 (0.57, 3.86)
3 +	15.0 % (3/20)	16.59 (2.80, 98.23)	4.5 % (1/22)	0.54 (0.06, 5.07)	0 % (0/4)	-	8.7 % (4/46)	2.12 (0.63, 7.23)
Total	2.2 % (15/670)		6.9 % (34/492)		7.2 % (12/166)		4.6 % (61/1,328)	

Table 7. Wheezing or whistling in the chest: lifetime prevalence and adjusted odds ratios (aOR)

Siblings	Newborns N= 670		Toddlers N = 566		Schoolchildren N = 214		All children N = 1,450	
	Crude Prevalence	aOR (95% CI)	Crude Prevalence	aOR (95% CI)	Crude Prevalence	aOR (95% CI)	Crude Prevalence	aOR (95% CI)
None	18.8 % (75/399)	1.00 (reference)	40.4 % (61/151)	1.00 (reference)	56.1 % (23/41)	1.00 (reference)	26.9 % (159/591)	1.00 (reference)
1	28.5 % (57/200)	1.92 (1.26, 2.94)	49.8 % (161/323)	1.37 (0.91, 2.07)	42.1 % (56/133)	0.44 (0.20, 0.97)	41.8 % (274/656)	1.45 (1.11, 1.89)
2	25.5 % (13/51)	1.59 (0.77, 3.29)	48.4 % (31/64)	1.07 (0.57, 2.00)	42.4 % (14/33)	0.45 (0.16, 1.28)	39.2 % (58/148)	1.21 (0.81, 1.83)
3 +	40.0 % (8/20)	2.06 (0.71, 5.97)	35.7 % (10/28)	0.53 (0.22, 1.32)	71.4 % (5/7)	0.99 (0.15, 6.52)	41.8 % (23/55)	1.11 (0.60, 2.04)
Total	22.8 % (153/670)		46.5 % (263/566)		45.8 % (98/214)		35.4 % (514/1,450)	

Table 8. **Doctor's diagnosis of eczema by sibling number (in the last 12 months for toddlers and schoolchildren, in the last 6 months for newborns): crude incidence and adjusted odds ratios (aOR)**

Siblings	Newborns N= 670		Toddlers N = 429		Schoolchildren N = 140		Toddlers and Schoolchildren N = 569	
	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)
None	7.0 % (28/399)	1.00 (reference)	6.8 % (8/117)	1.00 (reference)	12.5 % (3/24)	1.00 (reference)	7.8 % (11/141)	1.00 (reference)
1	12.5 % (25/200)	2.09 (1.15, 3.81)	3.7 % (9/241)	0.48 (0.17, 1.34)	1.11 % (1/90)	0.09 (0.00, 1.08)	3.0 % (10/331)	0.34 (0.14, 0.86)
2	13.7 % (7/51)	1.99 (0.77, 5.12)	13.7 % (7/51)	1.91 (0.59, 6.16)	0 % (0/20)	-	9.9 % (7/71)	1.21 (0.42, 3.82)
3 +	30.0 % (6/20)	3.95 (1.18, 13.16)	5.0 % (1/20)	0.75 (0.07, 7.52)	0 % (0/6)	-	3.8 % (1/26)	0.42 (0.05, 3.81)
Total	9.8 % (66/670)		5.8 % (25/429)		2.8 % (4/140)		5.1 % (29/569)	

Table 9. **Doctor's diagnosis of hay fever in the last 12 months by sibling number: crude incidence and adjusted odds ratios (aOR)**

Siblings	Toddlers N = 537		Schoolchildren N = 173		Toddlers and Schoolchildren N = 710	
	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)
None	3.5 % (5/142)	1.00 (reference)	20.0 % (7/35)	1.00 (reference)	6.8 % (12/177)	1.00 (reference)
1	3.2 % (10/308)	1.00 (0.33, 3.05)	11.4 % (12/105)	0.46 (0.16, 1.37)	5.3 % (22/413)	0.72 (0.34, 1.53)
2	6.7 % (4/60)	2.22 (0.53, 9.22)	11.5 % (3/26)	0.62 (0.12, 3.15)	8.1 % (7/86)	1.25 (0.43, 3.64)
3 +	0 % (0/27)	-	14.3 % (1/7)	1.03 (0.08, 12.77)	2.9 % (1/34)	0.64 (0.07, 5.57)
Total	3.5 % (19/537)		13.3 % (23/173)		5.9 % (42/710)	

Table 10. Doctor's diagnosis of food allergy by sibling number (in the last 12 months for toddlers and schoolchildren, in the last 6 months for newborns) : crude incidence and adjusted odds ratios (aOR)

Siblings	Newborns N= 670		Toddlers N = 448		Schoolchildren N = 139		Toddlers and Schoolchildren N = 587	
	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)
None	2.8 % (11/399)	1.00 (reference)	1.7 % (2/118)	1.00 (reference)	8.7 % (2/23)	1.00 (reference)	2.8 % (4/141)	1.00 (reference)
1	4.0 % (8/200)	1.54 (0.58, 4.01)	2.7 % (7/258)	1.77 (0.28, 11.16)	2.2 % (2/90)	0.12 (0.01, 1.20)	2.6 % (9/348)	0.69 (0.17, 2.80)
2	3.9 % (2/51)	1.20 (0.24, 6.13)	5.7 % (3/53)	3.21 (0.32, 32.23)	0 % (0/19)	-	4.2 % (3/72)	1.53 (0.23, 10.14)
3 +	5.0 % (1/20)	0.87 (0.09, 8.48)	0 % (0/19)	-	0 % (0/7)	-	0 % 0/26	-
Total	3.3 % (22/670)		2.7 % (12/448)		2.8 % (4/139)		2.7 % (16/587)	

Table 11. Sensitisation to dust mites by number of older siblings: 12-months crude incidence and adjusted odds ratios (aOR)

Older Siblings	Newborns N = 622		Toddlers N = 536		Schoolchildren N = 213		All children N = 1,371	
	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)
None	4.3 % (16/376)	1.00 (reference)	6.0 % (15/248)	1.00 (reference)	3.3 % (4/122)	1.00 (reference)	4.7 % (35/746)	1.00 (reference)
1	2.8 % (5/181)	0.61 (0.22, 1.75)	4.1 % (9/221)	0.55 (0.22, 1.34)	7.8 % (6/77)	2.59 (0.69, 9.69)	4.2 % (20/479)	0.84 (0.47, 1.50)
2	2.2 % (1/45)	0.55 (0.07, 4.37)	7.7 % (4/52)	1.20 (0.35, 4.17)	18.2 % (2/11)	6.66 (1.02, 43.70)	6.5 % (7/108)	1.40 (0.59, 3.13)
3 +	10.0 % (2/20)	4.10 (0.70, 24.05)	13.3 % (2/15)	1.78 (0.30, 10.75)	0 % (0/3)	-	10.5 % (3/38)	2.11 (0.65, 6.85)
Total	3.8 % (24/622)		5.6 % (30/536)		5.6 % (12/213)		4.8 % (66/1,371)	

Table 12. Lifetime prevalence of asthma by number of older siblings: crude prevalence and adjusted odds ratios (aOR)

Older Siblings	Newborns N= 670		Toddlers N = 566		Schoolchildren N = 214		All children N = 1,450	
	Crude Prevalence	aOR (95% CI)	Crude Prevalence	aOR (95% CI)	Crude Prevalence	aOR (95% CI)	Crude Prevalence	aOR (95% CI)
None	0.0 % (4/407)	1.00 (reference)	16.2 % (43/266)	1.00 (reference)	26.8 % (33/123)	1.00 (reference)	10.0 % (80/796)	1.00 (reference)
1	2.1 % (4/194)	2.02 (0.50, 8.23)	22.4 % (52/232)	1.34 (0.82, 2.18)	28.6 % (22/77)	1.03 (0.52, 2.03)	15.5 % (78/503)	1.55 (1.05, 2.27)
2	8.2 % (4/49)	8.47 (2.02, 35.56)	17.0 % (9/53)	1.01 (0.44, 2.31)	36.4 % (4/11)	1.70 (0.42, 6.90)	15.0 % (17/113)	1.70 (0.89, 3.25)
3 +	15 % (3/20)	14.43 (2.78, 74.97)	26.7 % (4/15)	1.41 (0.40, 5.03)	33.3 % (1/3)	1.19 (0.08,17.76)	21.0 % (8/38)	2.52 (0.99, 6.44)
Total	2.2 % (15/670)		18.5 % (105/566)		28.0 % (60/214)		12.6 % (183/1,450)	

Table 13. 12 months asthma incidence by number of older siblings: crude incidence and adjusted odds ratios (aOR)

Older Siblings	Newborns N= 670		Toddlers N = 492		Schoolchildren N = 166		All children N = 1,328	
	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)
None	0.0 % (4/407)	1.00 (reference)	5.9 % (14/237)	1.00 (reference)	5.3 % (5/95)	1.00 (reference)	3.1 % (23/739)	1.00 (reference)
1	2.1 % (4/194)	2.02 (0.50, 8.23)	8.6 % (17/197)	1.44 (0.66, 3.14)	9.8 % (6/61)	1.94 (0.55, 6.86)	6.0 % (27/452)	2.04 (1.11, 3.76)
2	8.2 % (4/49)	8.47 (2.02, 35.56)	4.3 % (2/46)	0.70 (0.15, 3.29)	12.5 % (1/8)	4.11 (0.32, 52.65)	6.8 % (7/103)	2.61 (1.01, 6.72)
3 +	15.0 % (3/20)	14.43 (2.78, 74.97)	8.3 % (1/12)	1.13 (0.12, 10.22)	0.0% (0/2)	-	11.8 % (4/34)	4.58 (1.26, 6.72)
Total	2.2 % (15/670)		6.9 % (34/492)		7.2 % (12/166)		4.6 % (61/1,328)	

Table 14. Wheezing or whistling in the chest by number of older siblings: lifetime prevalence and adjusted odds ratios (aOR)

Older Siblings	Newborns N= 670		Toddlers N = 566		Schoolchildren N = 214		All children N = 1,450	
	Crude Prevalence	aOR (95% CI)	Crude Prevalence	aOR (95% CI)	Crude Prevalence	aOR (95% CI)	Crude Prevalence	aOR (95% CI)
None	18.9 % (77/407)	1.00 (reference)	42.5 % (113/266)	1.00 (reference)	43.1 % (53/123)	1.00 (reference)	30.5 % (243/796)	1.00 (reference)
1	28.9 % (56/194)	1.81 (1.19, 2.73)	53.0 % (123/232)	1.32 (0.91, 1.92)	46.7 % (36/77)	1.16 (0.64, 2.08)	42.7 % (215/503)	1.55 (1.20, 2.00)
2	24.5 % (12/49)	1.23 (0.60, 2.53)	41.5 % (22/53)	0.89 (0.48, 1.66)	63.6 % (7/11)	2.24 (0.60, 8.33)	36.3 % (41/113)	1.24 (0.79, 1.95)
3 +	40.0 % (8/20)	1.75 (0.65, 2.53)	33.3 % (5/15)	0.57 (0.18, 1.81)	66.7 % (2/3)	2.29 (0.19, 27.77)	39.5 % (15/38)	1.30 (0.62, 2.73)
Total	22.8 % (153/670)		46.5 % (263/566)		45.8 % (98/214)		35.4 % (514/1,450)	Total

Table 15. Doctor's diagnosis of eczema by number of older siblings (in the last 12 months for toddlers and schoolchildren, in the last 6 months for newborns): crude incidence and adjusted odds ratios (aOR)

Older Siblings	Newborns N= 670		Toddlers N = 429		Schoolchildren N = 140		Toddlers and Schoolchildren N = 569	
	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)
None	7.1 % (29/407)	1.00 (reference)	5.9 % (12/204)	1.00 (reference)	3.9 % (3/76)	1.00 (reference)	5.4 % (15/280)	1.00 (reference)
1	12.4 % (24/194)	1.92 (1.07, 3.44)	3.5 % (6/172)	0.48 (0.17, 1.34)	1.8 % (1/54)	0.49 (0.05, 4.93)	3.1 % (7/226)	0.50 (0.19, 1.30)
2	14.3 % (7/49)	1.86 (0.75, 4.57)	16.7 % (7/42)	2.66 (0.93, 7.60)	0.0 % (0/7)	-	14.3 % (7/49)	2.61 (0.88, 7.73)
3 +	30.0 % (6/20)	3.69 (1.22, 11.18)	0.0 % (0/11)	-	0.0 % (0/3)	-	0.0 % (0/14)	-
Total	9.8 % (66/670)		5.8 % (25/429)		2.8 % (4/140)		5.1 % (29/569)	Total

Table 16. Doctor's diagnosis of hay fever in the last 12 months by number of older siblings: crude incidence and adjusted odds ratios (aOR)

Older Siblings	Toddlers N = 537		Schoolchildren N = 173		Toddlers and Schoolchildren N = 710	
	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)
None	4.3 % (11/254)	1.00 (reference)	15.0 % (15/100)	1.00 (reference)	7.3 % (26/354)	1.00 (reference)
1	2.3 % (5/220)	0.52 (0.17, 1.57)	13.1 % (8/61)	0.86 (0.34, 2.19)	4.6 % (13/281)	0.88 (0.42, 1.86)
2	6.1 % (3/49)	1.41 (0.37, 5.48)	0.0 % (0/9)	-	5.2 % (3/58)	1.20 (0.32, 4.48)
3 +	0.0 % (0/14)	-	0.0 % (0/3)	-	0.0 % (0/17)	-
Total	3.5 % (19/537)		13.3 % (23/173)		5.9 % (42/710)	

Table 17. Doctor's diagnosis of food allergy by number of older siblings (in the last 12 months for toddlers and schoolchildren, last 6 months for newborns): crude incidence and adjusted odds ratios (aOR)

Older Siblings	Newborns N= 670		Toddlers N = 448		Schoolchildren N = 139		Toddlers and Schoolchildren N = 587	
	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)	Crude Incidence	aOR (95% CI)
None	2.7 % (11/407)	1.00 (reference)	2.4 % (5/210)	1.00 (reference)	3.7 % (3/81)	1.00 (reference)	2.7 % (8/291)	1.00 (reference)
1	4.1 % (8/194)	1.55 (0.61, 3.97)	2.7 % (5/187)	1.24 (0.31, 4.95)	2.1 % (1/48)	0.50 (0.05, 5.11)	2.5 % (6/235)	0.68 (0.17, 2.67)
2	4.1 % (2/49)	1.38 (0.29, 6.50)	4.9 % (2/41)	3.55 (0.55, 22.94)	0.0 % (0/7)	-	4.2 % (2/48)	1.41 (0.20, 9.88)
3 +	0.0 % (1/20)	1.06 (0.12, 9.30)	0.0 % (0/10)	-	0.0 % (0/3)	-	0.0 % (0/13)	-
Total	3.3 % (22/670)		2.7 % (12/448)		2.8 % (4/139)		2.7 % (16/587)	

Chapter 6

DISCUSSION

The number of siblings has been shown to be inversely related to the prevalence of atopic disorders such as asthma, hay fever, eczema or sensitization. This observation led Strachan to propose that infections in early childhood might protect against atopy (Strachan 1989). A mechanism has been proposed by which early infection by viruses or bacteria, through the preferential induction of Th1-type cytokines, could prevent atopic sensitization. More direct evidence that childhood infection might prevent atopy comes from a cohort study in Guinea-Bissau, West Africa, which found that young adults who had experienced measles in childhood during a severe epidemic were significantly less likely to be atopic than those who had been vaccinated and did not have measles (Shaheen et al. 1996). Other infections were also found to protect against allergies: Italian military students who were seropositive for hepatitis A were less likely to be atopic and to have atopic disease than those who were seronegative (Matricardi et al. 1997), and adult seropositivity for hepatitis A is likely to be a marker of predominantly childhood infection, in particular infections with fecal-oral transmission.

The findings of the present study do not confirm the formulated hypotheses that the number of siblings or birth order (number of older siblings) has a protective effect against sensitization or atopic manifestations, although

the results are consistent with other studies who selected their populations in a similar way. One study who selected their higher risk population based on family history of atopy failed to find an association between family size and atopy (Burr et al. 1997). Another study who found a protective effect of number of siblings on atopy for the total population failed to find the same effect when they only looked at subjects who reported parental allergy (Svanes et al. 1999). For our cohort only children with family history of atopy were recruited, and at least one parent had to be sensitized to at least one tested allergen, thus selecting children at higher risk for developing atopies.

There might be several explanations why the sibling effect is absent in subjects with family history of atopy. One of the hypotheses is that environmental factors related to childhood may have a smaller potential to influence the development of the immune system in an allergic or non-allergic direction in subjects who already have a high genetic predisposition for allergic disease. Therefore even if the sibling effect is present in the original population, it may disappear when the population is selected based on family history of atopic disorders.

Another explanation would be that the sibling effect may be due entirely to differential reporting bias: parents with less children are more likely to observe atopic symptoms than parents with a high number of children, causing a spurious correlation. The disappearance of the effect in the "high risk" families may be explained by an increased alertness of the parents who have allergies

themselves, even in the case of large families. But this scenario would only apply to symptoms measured by questionnaires and not to SPT or IgE measurements.

The absence of the sibling effect for wheezing and asthma in "higher risk" children could be also explained by a tendency of children from larger families to experience more viral infections that may trigger wheezing, thus counterbalancing a possible inverse relationship between sibship size and allergic asthma.

A situation that may work against the "sibling effect" is the fact that in families with a large number of siblings there may be a higher exposure to allergens present in the house dust (e.g. house dust mite allergens) because of a higher activity in the house. If this situation comes together with a family history of atopy, then those children will have a higher risk of developing an atopy, and the absence of the "sibling effect" for this selected group may be explained in this way.

Another possibility for bias may result from the process of selecting the higher risk population. Theoretically, by screening the children for a family history of atopy we are trying to select more children who will develop an atopic disease, therefore we may say that we used a screening test with a certain specificity and sensitivity in order to select "cases". If this screening test would have a very high specificity and sensitivity for example, then virtually only cases would be selected and any effect that would be present in the original population would disappear in the selected population. For lower specificities and sensitivities a bias towards

the null value will still exist, therefore diminishing the probability of finding an existing association.

Chapter 7

CONCLUSION

The present work does not support the hypothesis that a large number of siblings is inversely associated with sensitization to mite allergens or atopic manifestations for this population of children at higher risk of developing atopic disorders. The findings are consistent with two other studies that selected their study populations in a similar way. The absence of the "sibling effect" in a higher risk population may be due to the fact that children with family history of atopy have a strong genetical predisposition to atopic manifestations and the protective effect of a large number of siblings is not effective. Other explanations speculate selection bias, reporting bias and exposure misclassification. The findings of the present study encourage further research in order to explain the phenomenon behind the "sibling effect", which may provide one of the most important clues to the causes and prevention of allergic disorders.

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