

Original article

Are atopy and specific IgE to mites and molds important for adult asthma?

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Background: Atopy is known to be important for childhood asthma, but this is to our knowledge the first study on its relation with development of asthma in adulthood.

Objectives: We addressed the role of atopy, measured as total IgE and Phadiatop, and of specific IgE antibodies to mites and molds in development of adult-onset asthma.

Methods: A population-based incident case-control study was conducted in the Pirkanmaa District in Southern Finland. All new clinically diagnosed cases of asthma 21-63 years of age were recruited 1997-2000 in the study district. A random sample of the source population formed the controls. A total of 485 cases and 665 controls provided a serum sample. Diagnosis of asthma was based on demonstration of reversibility in lung function investigations. Subjects with previous asthma were excluded. Phadiatop score and IgE antibodies were analyzed with the UniCAP system.

Results: The adjusted odds ratio of asthma increased with total IgE and Phadiatop score in a dose-dependent pattern. IgE antibodies to house dust mite and storage mite were significantly related to an increased risk of asthma. Among molds, increased risk of asthma was seen in relation to IgE antibodies to *Aspergillus fumigatus* and *Cladosporium herbarum*. Population attributable fraction due to sensitization to common aeroallergens was 30% (95% CI, 23-41).

Conclusion: Atopy is a strong determinant of asthma in adulthood. Specific IgE antibodies to mites and some molds are significantly related to increased risk of adult-onset asthma. A considerable fraction of adult asthma could be prevented by measures to reduce atopy. (J Allergy Clin Immunol 2006;117:1103-1110.)

Key words: Atopy, asthma, IgE antibodies, case-control study, general population, molds, mites, Phadiatop

Abbreviations used

AF_{exp}: Attributable fraction
 AF_{pop}: Population attributable fraction
 ECRHS: European Community Respiratory Health Survey
 OR: Odds ratio
 PEF: Peak expiratory flow

A considerable increase in asthma has been observed over the past decades, although since the 1990s some leveling off has been reported.¹⁻⁵ Atopy is known to be an important factor for asthma in childhood,⁶ but its importance for new-onset asthma in adults has not been addressed before to our knowledge, although both atopy and asthma are common in working-age populations. A few cross-sectional or prevalent case-control studies have investigated the risk of asthma related to some specific IgE antibodies,^{7,8} but the previous studies did not distinguish new-onset asthma from exacerbation of an existing disease that may have developed already in childhood.

We showed previously that occurrence of indoor molds at work is significantly related to an increased risk of incident asthma in adults, with an odds ratio (OR) of 1.54.⁹ When analyzing IgG antibodies to a panel of 8 microbes as indicators of exposure to molds and bacteria, IgG antibodies to *Trichoderma citrinoviride* were related to the risk of asthma.¹⁰ Several agents in indoor dampness situations have been suggested to induce asthma, including molds, bacteria, dust mites, and chemicals emitted from damp materials, but the mechanisms by which these agents act are not yet well understood.^{11,12}

We conducted a large population-based incident case-control study to assess the role of total IgE and Phadiatop (Pharmacia Diagnostics, Uppsala, Sweden) score as indicators of atopy for the development of adult-onset asthma, and to investigate the relations between specific IgE antibodies to mites and molds and incident adult asthma in a working-age population. We also assessed the population attributable fraction (AF_{pop}) of asthma due to sensitization to common aeroallergens. Our focus on specific IgE antibodies to molds and mites was based on our interest in allergens that could be avoided, but also on the fact that since the early 1990s, the Finnish Register of Occupational Diseases showed an emerging "epidemic" of occupational asthma caused by indoor molds and mites (mainly storage mites).

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TABLE I. Diagnostic criteria for asthma¹⁵

1. Occurrence of at least one asthma-like symptom: prolonged cough, wheezing, attacks of or exercise-induced dyspnea, or nocturnal cough or wheezing

and

2. Demonstration of reversibility in airway obstruction in lung function tests:

Significant improvement in response to short-acting bronchodilating medication in a bronchodilator test. The criteria for significant changes were:

- $FEV_1 \geq 15\%$
- Forced vital capacity $\geq 15\%$
- PEF $\geq 23\%$

and/or

$\geq 20\%$ daily variation* and/or $\geq 15\%$ improvement* in response to short-acting bronchodilating medication during at least two days in a 2-week diurnal PEF follow-up

and/or

Significant improvement in spirometric lung function (for % criteria see above) and/or $\geq 20\%$ improvement in the average PEF level in response to a 2-week oral steroid treatment

*Calculated according to the standard practice of the Tampere University Hospital¹⁵: maximum daily variation = (highest PEF value during the day – lowest PEF value during the day)/ highest PEF value during the day; bronchodilator response = (highest PEF value after bronchodilating medication – highest PEF value before medication)/ highest PEF value before medication.

METHODS

Study design

This study was a population-based case-control study of incident asthma cases. The source population consisted of adults 21 to 63 years of age living in the Pirkanmaa District, which is a geographically defined area in South Finland, with a population of 440,913 in 1997.^{9,10,13,14} This study was approved by the ethics committees of the Finnish Institute of Occupational Health and the Tampere University Hospital.

Definition and selection of cases

We recruited systematically all new cases of asthma diagnosed clinically in the city of Tampere from September 1997, and in the whole Pirkanmaa District from March 1998 to April 2000. Patients were recruited at all health care facilities diagnosing asthma, including the Department of Pulmonary Medicine at the Tampere University Hospital, offices of private-practicing pulmonary physicians, as well as public health care centers. To ensure participation of those patients with asthma not identified by this thorough system, the National Social Insurance Institution of Finland performed a computerized search of all patients who had received reimbursement rights for asthma medication during the study period and who had not yet participated.

The diagnostic criteria of asthma included occurrence of at least 1 asthma-like symptom and demonstration of reversible airways obstruction in lung function investigations (Table I).^{9,10,13-15} At the Tampere University Hospital, potential cases were recruited at their first visit because of suspect asthma, and diagnosis was then verified in clinical examinations. At the other health care facilities, cases were recruited immediately when their asthma diagnosis was confirmed. The National Social Insurance Institution invited cases identified by them to participate in the study 0.5-2 years after their diagnosis was established. For these patients, the date and criteria of the asthma diagnosis were confirmed from their medical records to ensure that their diagnosis fulfilled our criteria.

Eligible subjects were invited to participate in the study, and informed consent was requested by their physician or through a letter sent by the National Social Insurance Institution at the time of

recruitment into the study. The medical records of all cases were checked, and only those with no previously diagnosed asthma or long-term use of any asthma medication were included in the study. A total of 521 cases (response rate, 86%) participated in the study. Of these, 485 cases (93%) provided a serum sample.

Selection of controls

Controls were randomly drawn from the source population (residents of Pirkanmaa 21-63 years old) using the national population registry, which has full coverage of the population. Recruitment took place by a letter at regular intervals throughout the study period. Altogether, 1016 controls participated in the study (response rate, 80%). After excluding 76 persons reporting previous or current asthma (7.5%), 6 persons older than 63 years (0.6%), and 2 returning incomplete questionnaires (0.2%), the number of controls was 932. Of these, 665 (71%) gave a serum sample.

Assessment of atopy

Total IgE and Phadiatop score were analyzed from the serum sample as indicators of atopy. Phadiatop score is based on specific IgE antibodies to common aeroallergens, including birch, timothy grass, ragweed, cat, dog, horse, *Dermatophagoides pteronyssinus*, and *Aspergillus fumigatus*. In addition, specific IgE antibodies to mites *Dermatophagoides pteronyssinus* and *Acarus siro*, and to molds *Aspergillus fumigatus*, *Cladosporium herbarum*, *Mucor racemosus*, *Penicillium notatum*, *Phoma betae*, and *Stachybotrys atra* were analyzed as indicators of specific allergies of interest. These were chosen on the basis of their suggested importance in indoor dampness problem situations.^{9,12,16}

Measurement methods

Questionnaire. All participants (cases and controls) answered a self-administered questionnaire, modified from the Helsinki Office Environment Study questionnaire for use in a general population and described in detail in previous publications.^{9,10,13,14,17,18} It included 6 sections: (1) personal characteristics, (2) current health information and medical history, (3) active smoking and environmental tobacco smoke exposure, (4) occupation and work environment, (5) home environment, and (6) dietary questions.

IgE antibody analyses. Participants gave serum samples at the laboratories of the Centre for Laboratory Medicine, Tampere University Hospital. Serum was separated by centrifugation and stored at -20°C before shipping to Finnish Institute of Occupational Health in Helsinki for IgE antibody analyses. Total IgE, Phadiatop score, and specific IgE antibodies to mites and molds were analyzed by the immunoassay system Pharmacia UniCAP (Pharmacia Diagnostics Ab, Uppsala, Sweden; www.unicapinvitrosight.com).¹⁹ Phadiatop was expressed as a score from 0-6 as graded by the UniCAP Phadiatop system, with the limits as follows: score 0 = 0-0.34 kU/L, score 1 = 0.35-0.69 kU/L, score 2 = 0.70-3.49 kU/L, score 3 = 3.50-17.4 kU/L, score 4 = 17.5-49.9 kU/L, score 5 = 50-100 kU/L, and score 6 = greater than 100 kU/L. Total IgE and specific IgE antibodies were expressed as kU/L, with values <0.35 defined as negative.

Lung function measurements. The same diagnostic protocol was applied for all patients with suspect asthma (Table I).^{9,10,13-15} The baseline spirometry and bronchodilation test were recorded with a pneumotachograph spirometer connected to a computer and using a disposable flow transducer (Medikro 905; Medikro, Kuopio, Finland) according to the standards of the American Thoracic Society.²⁰ Presence of obstruction was judged by using the reference values derived from a Finnish population.²¹ All patients performed peak expiratory flow (PEF) follow-up with measurements twice a day for at least 2 weeks using a mini-Wright meter. During the second week, measurements were taken before and 15 minutes after short-acting bronchodilating medication. A 2-week oral steroid treatment with 20 mg prednisolone was carried out for those with a strong suspicion of asthma, if the other diagnostic tests were negative. The patient performed 2 weeks of PEF follow-up during this treatment and a spirometry at the end of the treatment period to judge the response.

Statistical methods

Statistical analyses were performed by using SAS statistical package (SAS Institute Inc, Cary, NC).²² We used exposure OR to quantify the relations between IgE antibodies and incident asthma, estimated in logistic regression analysis adjusting for 5 core covariates: sex, age, education (as an indicator of socioeconomic status), personal smoking status, and exposure to environmental tobacco smoke at home and at work. We did not adjust for any covariates that could be in the causal pathway (eg, parental atopy, exposure to molds or pets). We divided total IgE level into 4 quartiles and compared the risk of asthma in the higher quartiles (quartile 2: >16 -39.1 kU/L; quartile 3: >39.1 kU/L to <107 kU/L; quartile 4: ≥ 107 kU/L) with the lowest quartile 1 (0-16 kU/L) as the reference category. Phadiatop was expressed as a score reflecting the IgE antibody levels to common aeroallergens, and the risk of asthma in higher scores was compared with the score 0 (the reference category). Analyses were also performed including both of these indicators of atopy simultaneously in the model to assess their independent effects. Specific IgE antibodies were dichotomized into negative (antibody concentration <0.35 kU/L, the reference category) and positive (antibody concentration ≥ 0.35 kU/L), and the positive values were further categorized into low (0.35 to <1.0 kU/L) and high levels (≥ 1.0 kU/L). In cluster analysis of specific IgE antibodies to mites and molds, mites formed a cluster and molds formed a separate cluster. Adjusting individual mites or molds for each other led to problems of collinearity; thus, we formed new variables for occurrence of antibodies to either of the 2 mites (any mite) and for any of the 6 molds (any mold). To assess the independent effect of mites, adjustment was made for any mold, and vice versa.

We quantified the effect of atopy on incidence of asthma in adults as an attributable fraction²³ or etiologic fraction,²⁴ providing the fraction of atopic cases for whom the disease was attributable to atopy.²⁴ The attributable fraction (AF_{exp}) was calculated as follows: $AF_{\text{exp}} =$

TABLE II. Characteristics of the study population, the Finnish Environment and Asthma Study 1997-2000

Characteristic	Cases		Controls	
	N	%	N	%
Total	485		665	
Sex				
Man	160	33.0	297	44.7
Woman	325	67.0	368	55.3
Age (y)				
21-29	98	20.2	84	12.6
30-39	98	20.2	162	24.4
40-49	121	25.0	194	29.2
50-59	130	26.8	172	25.9
60-63	38	7.8	53	8.0
Parental allergic diseases	169	34.9	149	22.4
Education*				
No vocational schooling	98	20.3	106	16.0
Vocational course	82	17.0	72	10.9
Vocational institution	140	29.0	187	28.2
College-level education	106	22.0	198	29.9
University or corresponding	57	11.8	100	15.1
Smoking†				
Never	225	46.7	345	52.0
Ex	125	25.9	156	23.5
Current	132	27.4	163	24.6
ETS				
At work	83	17.1	92	13.8
At home	29	6.0	38	5.7
Pets at home sometimes	341	70.3	449	67.5
Indoor mold exposure at work or at home	111	22.9	154	23.2
Any work exposure‡	295	60.8	427	64.2

*Information on education was missing for 4 subjects.

†Information on smoking was missing for 4 subjects.

‡Self-reported exposure to sensitizers, dusts, and/or fumes.

($OR - 1$)/ OR , where OR is the adjusted odds ratio related to atopy, an unbiased estimate of incidence rate ratio in a population-based case-control study.²⁴ The OR was obtained from an analysis including Phadiatop as a dichotomous variable (0 if Phadiatop score = 0, 1 if Phadiatop score > 0), while adjusting for the core covariates. The 95% CI was calculated by using the corresponding interval of OR . We also estimated the AF_{pop} :²⁴

$$AF_{\text{pop}} = p_{\text{cases}} AF_{\text{exp}}$$

where p_{cases} is the proportion of cases with Phadiatop score > 0 . The 95% CI was estimated as described by Greenland.²³

RESULTS

Incidence of adult-onset asthma and characteristics and IgE antibodies of cases and controls

The prevalence of asthma (previous and current) in this working-age population was 7.5%. The incidence of adult-onset asthma during our study period was 0.90 per

TABLE III. Crude and adjusted OR of asthma in relation to the indicators of atopy

Atopy indicators	Cases (N = 485), %	Controls (N = 665), %	Crude OR (95% CI)	OR* (95% CI)	OR† (95% CI)
Total IgE					
First quartile	12.6	29.6	1.00	1.00	1.00
Second quartile	19.4	27.2	1.68 (1.15-2.45)	1.63 (1.10-2.41)	1.57 (1.06-2.32)
Third quartile	27.4	23.9	2.70 (1.87-3.90)	2.76 (1.89-4.05)	2.32 (1.56-3.46)
Fourth quartile	40.6	19.3	4.97 (3.46-7.15)	5.33 (3.64-7.80)	3.33 (2.18-5.08)
Phadiatop score					
0	55.0	76.4	1.00	1.00	1.00
>0-2	17.0	13.7	1.73 (1.24-2.41)	1.90 (1.34-2.70)	1.33 (0.92-1.93)
>2-4	22.0	9.2	3.33 (2.35-4.72)	4.14 (2.84-6.04)	2.51 (1.66-3.79)
>4	6.0	0.8	11.1 (4.25-29.1)	14.1 (5.21-38.2)	7.83 (2.75-22.3)

*OR adjusted for sex, age, education, smoking, and environmental tobacco smoke exposure.

†OR adjusted for sex, age, education, smoking, environmental tobacco smoke exposure, and the other atopy indicator.

1000 person-years. Table II presents the characteristics of cases and controls. Cases had higher levels of total IgE and higher Phadiatop scores than controls (Table III). Cases had also more frequently positive IgE antibodies to mites and molds compared with controls (Table IV).

Atopy and the risk of asthma

The risk of incident asthma increased in a dose-dependent pattern with increasing total IgE and increasing Phadiatop score (Table III). Adjusting each atopy indicator for the other reduced the effect estimates slightly, but exposure-effect patterns with strongly positive effects were still detected, indicating that their effects were largely independent.

Specific IgE antibodies and risk of asthma

Specific IgE antibodies to house dust mite *Dermatophagoides pteronyssinus* and storage mite *Acarus siro* were not very common, but when detected, they were related to a significantly increased risk of incident asthma (Table IV). Increased OR of asthma was detected also in relation to all 6 molds, with relations statistically significant for *Aspergillus fumigatus* and *Cladosporium herbarum*. The CIs for the other molds were rather wide because of a small number of subjects having antibodies to them. The risk of asthma related to the occurrence of either mite was significantly increased after adjusting for any molds, and the risk related to any mold was significantly increased after adjusting for either mite, suggesting that their effects were mainly independent of each other, although some reduction in effect estimates was observed after adjustment. The risk of new asthma increased with increasing IgE antibody levels to *Dermatophagoides pteronyssinus* and *Aspergillus fumigatus* (Fig 1).

Risk of adult-onset asthma attributable to atopy

The fraction of new adult-onset asthma attributable to IgE antibodies to common aeroallergens was 66% (95% CI, 55-74) among the atopic cases. The attributable

fraction in the whole working-age population was 30% (95% CI, 23-36).

DISCUSSION

To our knowledge, this study includes the largest number of asthma cases among all studies addressing the determinants of clinically verified adult-onset asthma published to date. The incident case-control study design is very efficient compared with a cohort study, which would yield a similar amount of information. With our asthma incidence rate of 0.9 cases per 1000 person-years, the current study corresponded to a follow-up of approximately 100,000 adults for 5.8 years (the denominator was approximately 581,000 person-years).

Our results showed that increases in the 2 atopy markers, total IgE and Phadiatop score, were related in a dose-dependent pattern with increasing risk of new adult-onset asthma. These findings suggest that atopy is a major determinant of development of asthma in adulthood and that the importance of atopy is not limited to childhood only. This has great importance for prevention, because both atopy and asthma are common in working-age populations.

When addressing the role of specific IgE antibodies to molds and mites for adult asthma, the strongest associations were detected with IgE antibodies to house dust mite, storage mite, and 2 molds, *Aspergillus fumigatus* and *Cladosporium herbarum*. Our results suggest that these specific sensitizations play a role in the development of adult-onset asthma, but only in a minority of patients with asthma, because their occurrence was rather low in this adult population. Of the specific sensitizations studied, IgE antibodies to house dust mite were detected most frequently (13.6%) among the cases of new asthma.

The fraction of new asthma attributable to atopy (defined as IgE antibodies to common aeroallergens) was 66% among atopic cases. The AF_{pop} , the fraction within the whole working age population, was rather high, 30%. This suggests that measures to reduce allergies could potentially prevent a considerable fraction of asthma developing in adulthood. As it is probably more difficult to

TABLE IV. Crude and adjusted OR of asthma in relation to specific IgE antibodies to mites and molds

Specific IgE Antibodies	Cases (N = 485), %	Controls (N = 665), %	Crude OR (95% CI)	OR* (95% CI)	OR† (95% CI)
<i>Dermatophagoides pteronyssinus</i>	13.6	6.9	2.12 (1.43-3.15)	2.30 (1.51-3.49)	
<i>Acarus siro</i>	10.3	6.0	1.80 (1.16-2.77)	1.80 (1.14-2.83)	
Any mite	14.9	8.6	1.86 (1.29-2.69)	1.98 (1.34-2.92)	1.74 (1.16-2.61)
<i>Aspergillus fumigatus</i>	5.4	2.1	2.63 (1.36-5.10)	2.73 (1.38-5.40)	
<i>Cladosporium herbarum</i>	2.3	0.6	3.83 (1.21-12.11)	4.69 (1.43-15.3)	
<i>Mucor racemosus</i>	1.9	0.8	2.50 (0.83-7.49)	2.65 (0.85-8.20)	
<i>Penicillium notatum</i>	3.1	1.7	1.90 (0.86-4.17)	2.11 (0.93-4.76)	
<i>Phoma betae</i>	2.5	1.5	1.66 (0.71-3.88)	1.85 (0.77-4.43)	
<i>Stachybotrys atra</i>	0.6	0.2	4.13 (0.43-39.8)	4.26 (0.43-42.6)	
Any mold	7.4	3.2	2.46 (1.42-4.27)	2.49 (1.40-4.42)	2.01 (1.11-3.67)

*OR adjusted for sex, age, education, smoking, and environmental tobacco smoke exposure.

†OR adjusted for sex, age, education, smoking, environmental tobacco smoke exposure, and either any mite or any mold.

prevent allergies to pollen, focus in the future should be on sources of allergens that could be reduced or avoided, such as pets and other domestic animals, and mites and molds related to indoor dampness problems. These findings are consistent with our previous results from questionnaire-based assessment, showing an increased risk of adult-onset asthma in relation to past keeping of pets¹³ and in relation to occurrence of visible mold or mold odor in the workplace.⁹ Effective preventive achievements may be accomplished in different ways in different health care systems. For example, health education on the risk of adult asthma in relation to keeping pets as well as in relation to indoor dampness problems could be distributed through the national primary care system and through the occupational health care system in Finland. This should be accompanied by information, such as in the form of booklets or television programs, on how to prevent indoor dampness problems. In the workplace, attention should be paid to prevention of indoor dampness and mold problems and to prompt repair of any damage that may have occurred. On the local administrative level, support in terms of financial aid and/or provision of know-how could be arranged for repairs of dampness problems in homes.

Validity issues

We were able to recruit a high proportion of all new cases with asthma in a geographically defined area by a thorough recruitment in the health care system and with the help of the National Social Insurance Institution. Patients were recruited at all health care facilities diagnosing asthma, including the Department of Pulmonary Medicine at the University Hospital, offices of private-practicing pulmonary physicians, and public health care centers. The response rate among the control subjects was also relatively high. Any major selection bias is thus unlikely in this study.

Assessment of atopy was based on objective measurements of total and specific IgE antibodies from serum samples. Serum samples were taken from a large majority of the cases before their asthma diagnosis was confirmed (at their first appointment because of a suspicion of asthma), and in others just at the same time, which ensures

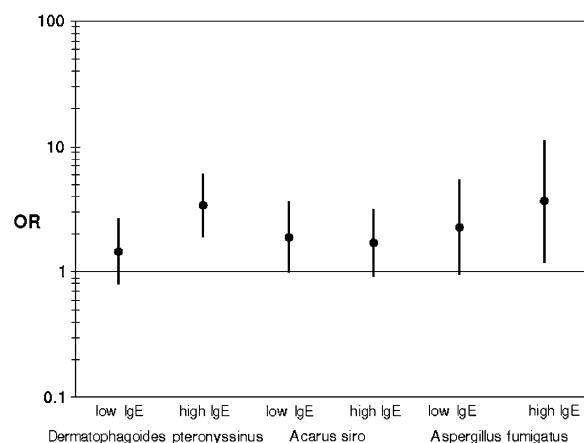


FIG 1. Adjusted OR (95% CI) of asthma in relation to specific IgE antibody levels to *Dermatophagoides pteronyssinus*, *Acarus siro*, and *Aspergillus fumigatus*. Low IgE level is 0.35 to <1.0 kU/L; high IgE level is ≥ 1.0 kU/L; these levels are compared with the reference category of <0.35 kU/L.

that atopy was present before asthma was diagnosed. Because sensitization does usually not develop overnight, it is likely that at least in the majority of our cases of new asthma sensitization preceded the onset of asthma. Naturally, development of sensitization and of asthma may have common determinants, so that sensitization either precedes development of asthma or is a concurrent process. IgE antibody analysis was performed by using a validated commercial UniCAP system.¹⁹ It is easier to conduct in a standardized way than skin testing. Phadiatop includes in Finland the following aeroallergens: birch, timothy grass, ragweed, cat, dog, horse, *Dermatophagoides pteronyssinus*, and *Aspergillus fumigatus*. The selection of this panel was made by the manufacturer and can be discussed, but it does reflect well the most common or otherwise important allergies in Finland. The sensitivity and specificity of Phadiatop has been evaluated in several studies by using a clinical diagnosis of atopy as the gold standard.^{19,25,26} In most of the studies, the clinical diagnosis was based on a history of atopic

symptoms, clinical investigation, and measurement of specific sensitizations to a panel of aeroallergens by either skin prick tests or RAST. Eriksson²⁵ found a sensitivity of 0.96, specificity of 0.94, and positive predictive value of 0.96 in 100 adults referred for allergy testing. This paper also reviewed 20 other studies providing information on sensitivity and specificity of Phadiatop and gave mean values of 0.91 and 0.93 for sensitivity and specificity, respectively. Matricardi et al²⁶ investigated 600 subjects randomly selected from attendants in an Italian Air Force training course. In their study, sensitivity was 99% and specificity 87%. Positive predictive value was only 54% because several subjects with positive specific IgE antibodies were asymptomatic. Paganelli et al¹⁹ combined results from 6 clinical studies including 894 study subjects. In their study, the sensitivity was 93% and specificity 89%.

Defining asthma on the basis of objective findings in extensive lung function measurements that were in accordance with the national guidelines¹⁵ was performed to eliminate information bias concerning the outcome—that is, the knowledge of atopic status of an individual did not affect the diagnosis. Such knowledge might cause bias when relying purely on doctor-diagnosed asthma or on symptom reports. Because of the national health care system and reimbursement system of asthma medications in Finland, we can be quite confident that we were able to identify and exclude those with previous asthma or long-term use of asthma medications, giving us assurance that our asthma cases were new. Naturally, when studying an adult population, we did not have knowledge of possible occurrence of some mild respiratory symptoms in childhood, but in any case, we were able to exclude any previous asthma that would have required treatment. This excludes any significant bronchial hyperresponsiveness in childhood, although does not exclude completely a possibility of mild asthma in childhood.

We adjusted the relations between atopy indicators and incident asthma for several core confounders in logistic regression analysis to eliminate these factors, such as educational level and smoking, as potential explanations for our results.

Synthesis with previous knowledge

After performing a systematic Medline search, this study is to our knowledge the first to evaluate the role of atopy for the development of new asthma in adulthood. Some previous studies assessed the association between atopy and prevalent asthma^{7,8} but did not separate the effect of atopy on new asthma from that of aggravating a pre-existing disease. Pollart et al⁷ assessed the population fraction of asthma exacerbation attributable to having specific IgE to any of 5 allergens to be 56% among patients with asthma admitted to an emergency department. A Spanish substudy⁸ of the cross-sectional European Community Respiratory Health Survey (ECRHS) assessed the AF_{pop} of asthma (defined as current symptomatic bronchial hyperresponsiveness) due to specific IgE or skin prick tests to be 42%. They later repeated this assessment in

the whole ECRHS population and found highly variable results between different centers, with the AF_{pop} ranging from 4% in Estonia to 61% in Barcelona.²⁷ The AF_{pop} detected in our study, 30%, is within the range of these estimates, but it should be remembered that our outcome was new-onset asthma rather than exacerbation of existing asthma.

Specific IgE antibodies to house dust mite were a significant determinant of adult-onset asthma in our study, although the occurrence of this sensitization was rather low, ranging between 7% and 14%. Such an occurrence is consistent with that in other Nordic countries.²⁸ Previous cross-sectional studies have found significant associations between specific IgE antibodies to house dust mite and bronchial hyperresponsiveness in Norway,²⁹ the Netherlands,³⁰ and countries of the ECRHS.²⁸ IgE antibodies to storage mite also increased significantly the risk of new asthma in our study. This has relevance for occupational settings and has not been investigated in other studies. We also found that specific IgE antibodies to *Aspergillus fumigatus* and *Cladosporium herbarum* were significantly related to adult-onset asthma. These findings suggest that sensitization to molds could be an important mechanism leading to adult-onset asthma, although in only a minority of cases. The Spanish ECRHS substudy found a prevalence ratio of 2.28 for asthma in relation to IgE to *Cladosporium*.⁸ *Cladosporium herbarum* and *Alternaria alternata* were related to increased risk of current asthma in the subsequent analysis of the total ECRHS population,³¹ but other studies have not investigated IgE antibodies to molds as determinants of incident adult-onset asthma.

CONCLUSION

This large population-based study of incident asthma provides evidence that atopy, measured as total IgE and specific IgE antibodies to common aeroallergens, is a strong determinant of new-onset asthma in adulthood. In addition, specific IgE antibodies to mites *Dermatophagoides pteronyssinus* and *Acarus siro* significantly increase the risk of adult-onset asthma. IgE antibodies to 6 molds, especially *Aspergillus fumigatus* and *Cladosporium herbarum*, were also related to the development of asthma in adulthood. The results suggest that the importance of atopy is not limited to childhood only, but that measures to reduce atopic sensitization might prevent a considerable fraction of adult asthma.

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