

Letter to the Editor

Influence of heredity on asthma continues to adulthood

To the Editor:

Little is known about the role of heredity in the development of asthma in adulthood. According to our systematic review of literature focusing on the heredity of asthma, but excluding studies on individual genes, only 1 previous study, investigating a Taiwanese population, has focused on adult-onset asthma.¹

The objectives of this study were to investigate whether parental asthma increases the risk of developing adult-onset asthma and to estimate to which degree the asthma of siblings and/or children characterizes the risk of the person himself or herself developing asthma in adulthood.

This study was a population-based incident case-control study. We systematically recruited all new adult (21-63 years) asthma cases diagnosed during 1997-2000 in the Pirkanmaa Hospital District in South Finland.^{2,3} The diagnostic criteria for asthma were (1) occurrence of at least 1 asthmalike symptom and (2) demonstration of significant reversibility in airways obstruction in lung function investigations (see Table E1 in this article's Online Repository at www.jacionline.org).² To ensure that all the cases had asthma diagnosed for the first time, we selected only those with no previously diagnosed asthma or long-term use (defined as at least 3 months of regular use) of any asthma medication. A total of 521 cases participated (response rate 86%). Controls were randomly drawn from the source population, applying the general eligibility criteria. After excluding those with previous or current asthma, our study included 932 controls (73%).

The study subjects answered a self-administered questionnaire concerning their personal characteristics, health and family history of asthma, smoking and secondhand smoke exposure, occupation and work environment, home environment, and diet.²⁻⁶ Heredity was operationally defined as questionnaire-reported asthma in first-degree relatives.

Details of the study subject selection and other methods are provided in the Methods section in this article's Online Repository at www.jacionline.org. Altogether 477 cases and 842 controls with full information on the family history of asthma were included in this study. The study was approved by the ethics committees of the Finnish Institute of Occupational Health and the Tampere University Hospital.

Table I shows characteristics of the study population. The risk of adult-onset asthma was highest among those with both maternal and paternal asthma (Table II). Having only paternal asthma was associated with a higher risk than having only maternal asthma, and both were related to significantly increased risk of the study subject's personal asthma. The risk of developing adult-onset asthma was similarly increased among those having siblings with asthma and those having children with asthma (Table II). When the effect of parents' asthma was studied together with that related to siblings or children, the highest risk was associated with the combined group (Table II). The risk of asthma increased gradually according to the number of the types of first-degree relatives with asthma (see Table II; see Fig E1 in this article's Online Repository at www.jacionline.org).

TABLE I. Characteristics of the study population

Characteristic	n (%)	
	Cases	Controls
Totals	477 (36.2)	842 (63.8)
Sex		
Male	154 (32.3)	393 (46.7)
Female	323 (67.7)	449 (53.3)
Age (y)		
21-29	103 (21.6)	130 (15.4)
30-39	98 (20.5)	202 (24.0)
40-49	113 (23.7)	228 (27.1)
50-59	127 (26.6)	217 (25.8)
60-64	36 (7.5)	65 (7.7)
Siblings*	348 (73.0)	613 (72.8)
Children†	286 (60.0)	549 (65.2)
Education‡		
No vocational schooling	96 (20.1)	131 (15.6)
Vocational course	82 (17.2)	93 (11.0)
Vocational institute	134 (28.1)	245 (29.1)
College-level education	108 (22.6)	245 (29.1)
University or correspondence	56 (11.7)	124 (14.7)
Smoking§		
No	226 (47.4)	450 (53.4)
Former	123 (25.8)	181 (21.5)
Current, occasional	26 (5.5)	46 (5.5)
Current, regular	99 (20.8)	164 (19.5)
Pets at home sometimes	334 (70.0)	567 (67.3)
SHS in the workplace or at home	99 (20.8)	142 (16.9)
Any work exposure¶	288 (60.4)	532 (63.2)
Visible mold or mold odor in the workplace or at home	114 (23.9)	180 (21.4)

SHS, Secondhand smoke.

*Information of siblings missing for 7 cases and 13 controls.

†Information of children missing for 4 cases and 6 controls.

‡Information of education missing for 1 case and 4 controls.

§Information of smoking missing for 3 cases and 1 control.

||At least 1 cigarette a day or 25 g of pipe tobacco a month.

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

Rather strong effect estimates for parental heredity (odds ratios [ORs] ranging from 1.94 to 3.85) were seen for adult-onset asthma, thus implying that inherited susceptibility to asthma not only affects the likelihood of developing asthma as a child but also continues to modify the risk in working-age population. It is possible that some genetic effects manifest only at adult age, when individuals face different kinds of exposures that are absent in the childhood environment, such as work exposures. This points toward the possibility of gene-environment interactions. Our finding is unique, as there are no previous studies addressing the role of heredity in adult-onset asthma in Caucasian populations. In a recent meta-analysis based mainly on studies of childhood asthma, the OR of personal asthma related to paternal asthma was of similar magnitude as in our study of adult-onset asthma (2.44, 95% confidence interval [CI], 2.14-2.79, in the meta-analysis vs 2.53, 95% CI, 1.64-3.89, in our study), whereas the OR related to maternal asthma was stronger in the meta-analysis (3.04, 95% CI, 2.59-3.56) than in our study (1.94, 95% CI, 1.31-2.88).⁷ However, the findings on children may not be applicable to adult-onset asthma, as these differ in phenotypes and lifestyle and environmental exposures that are related to the

TABLE II. The risk of asthma in relation to asthma in first-degree relatives

Determinant	n (%)	Cases (%)	Controls (%)	OR Crude (95% CI)*	Adjusted OR (95% CI)*†	Adjusted OR (95% CI)*‡
Totals	1319 (100)	477 (36.2)	842 (63.8)			
Parental asthma						
No	1091 (82.7)	357 (74.8)	734 (87.2)	1.00	1.00	1.00
Paternal only	98 (7.4)	54 (11.3)	44 (5.2)	2.52 (1.66-3.83)	2.54 (1.65-3.91)	2.53 (1.64-3.89)
Maternal only	118 (8.9)	58 (12.2)	60 (7.1)	1.99 (1.36-2.91)	1.97 (1.33-2.91)	1.94 (1.31-2.88)
Both	12 (0.9)	8 (1.7)	4 (0.5)	4.11 (1.23-13.74)	4.04 (1.18-13.79)	3.85 (1.11-13.28)
Siblings with asthma§						
No	1140 (86.4)	391 (82.0)	749 (89.0)	1.00	1.00	1.00
Yes	159 (12.1)	79 (16.6)	80 (9.5)	1.96 (1.39-2.76)	1.80 (1.26-2.56)	1.83 (1.28-2.62)
Ratio of asthmatic/nonasthmatic siblings§ ¶						
None	1136 (86.1)	389 (81.6)	747 (88.7)	1.00	1.00	1.00
≤1/3	89 (6.7)	46 (9.6)	43 (5.1)	2.41 (1.49-3.90)	2.06 (1.25-3.38)	2.10 (1.28-3.47)
>1/3	69 (5.2)	32 (6.7)	37 (4.4)	1.70 (1.03-2.80)	1.63 (0.98-2.71)	1.67 (1.00-2.78)
Children with asthma						
No	1203 (91.2)	422 (88.5)	781 (92.8)	1.00	1.00	1.00
Yes	106 (8.0)	51 (10.7)	55 (6.5)	1.95 (1.29-2.94)	1.84 (1.21-2.82)	1.90 (1.24-2.92)
Ratio of asthmatic/nonasthmatic children#**††						
None	1202 (91.1)	421 (88.3)	781 (92.8)	1.00	1.00	1.00
≤1/2	87 (6.6)	41 (8.6)	46 (5.5)	2.04 (1.29-3.24)	1.94 (1.21-3.12)	2.00 (1.23-3.22)
>1/2	19 (1.4)	10 (2.1)	9 (1.1)	2.22 (0.89-5.5)	1.93 (0.76-4.91)	2.04 (0.80-5.23)
Parents and siblings combined§						
No	960 (72.8)	301 (63.1)	659 (78.3)	1.00	1.00	1.00
Parental only	180 (13.6)	90 (18.9)	90 (10.7)	2.19 (1.58-3.02)	2.21 (1.58-3.07)	2.19 (1.57-3.05)
Siblings only	117 (8.9)	52 (10.9)	65 (7.7)	1.81 (1.22-2.69)	1.67 (1.11-2.51)	1.72 (1.14-2.59)
Both	42 (3.2)	27 (5.7)	15 (1.8)	4.06 (2.12-7.78)	3.71 (1.91-7.20)	3.67 (1.89-7.15)
Parents and children combined#**						
No	1006 (76.3)	321 (67.3)	685 (81.4)	1.00	1.00	1.00
Parental only	197 (14.9)	101 (21.2)	96 (11.4)	2.23 (1.63-3.04)	2.22 (1.62-3.06)	2.18 (1.59-3.01)
Children only	81 (6.1)	35 (7.3)	46 (5.5)	1.83 (1.15-2.93)	1.73 (1.06-2.82)	1.77 (1.09-2.90)
Both	25 (1.9)	16 (3.4)	9 (1.1)	4.28 (1.86-9.85)	3.98 (1.71-9.29)	4.15 (1.77-9.74)
Parents, siblings, and children combined‡‡§§						
No	889 (67.4)	271 (56.8)	618 (73.4)	1.00	1.00	1.00
Parental only	159 (12.1)	77 (16.1)	82 (9.7)	2.12 (1.50-2.99)	2.15 (1.51-3.05)	2.11 (1.48-3.01)
Siblings only	103 (7.8)	46 (9.6)	57 (6.8)	1.92 (1.26-2.93)	1.77 (1.15-2.73)	1.84 (1.19-2.84)
Children only	67 (5.1)	29 (6.1)	38 (4.5)	1.98 (1.18-3.32)	1.89 (1.11-3.24)	1.96 (1.14-3.36)
Any 2	68 (5.2)	40 (8.4)	28 (3.3)	3.55 (2.13-5.92)	3.24 (1.92-5.45)	3.31 (1.96-5.61)
All 3	6 (0.5)	4 (0.8)	2 (0.2)	5.24 (0.95-28.91)	4.32 (0.78-24.08)	4.41 (0.79-24.60)

*Analyses where siblings and/or children were considered were adjusted either for having siblings (yes or no) and/or having children (yes or no), or for the number of siblings (0, 1-2, 3-4, >4) or children (0, 1-2, >2) (ratio analyses).

†Adjusted for age, sex, education, and smoking.

‡Adjusted for age, sex, education, smoking, secondhand smoke (work or home), pets, occupational exposure (except molds), visible mold, or mold odor (work or home).

§Information on siblings missing for 7 cases and 13 controls.

||Includes 338 subjects (122 cases and 216 controls) with no siblings.

¶Total number of siblings missing for 3 cases and 2 controls.

#Information of children missing for 4 cases and 6 controls.

**Includes 474 subjects (187 cases and 287 controls) with no children.

††Total number of children missing for 1 case.

‡‡Information for siblings and children missing for 10 cases and 17 controls.

§§Includes 652 subjects (248 cases and 404 controls) with no siblings and/or no children.

risk of asthma.⁸ For example, it has been reported that early-onset (before the age of 12 years) and late-onset (after the age of 12 years) severe asthma differ by presence of allergies, eosinophilia, and other inflammatory processes.⁹

Our systematic review revealed only 1 previous study on heredity and adult-onset asthma. Lee et al¹ studied 24,784 Taiwanese adults, of which 286 had new-onset asthma (symptoms within the preceding 5 years) based on questionnaire. The risk of adult-onset asthma associated with paternal asthma in their study (adjusted OR, 2.63, 95% CI, 1.55-4.24) was similar to that found in our study (2.53, 95% CI, 1.62-3.89). They found maternal asthma to be a stronger risk factor with the effect estimate

of 11.61 (95% CI, 8.07-16.42), which is higher than our effect estimate (1.94, 95% CI, 1.31-2.88). Several differences between the studies including the definition of asthma (symptom-based vs clinical lung function-based), categorization of parental asthma, and factors that were adjusted for in the analyses may explain the detected differences. In addition, the genetic composition of the Taiwanese and Finnish populations is expected to be quite different.

No previous study has addressed the role of other first-degree relatives in characterizing the risk of adult-onset asthma. The highest risk in our study was seen among those who had asthma present in several categories of first-degree family members

(parents, siblings, and/or children), thus indicating that in such families the asthma susceptibility is strongly present.

In our study, the possibility of selection bias is small due to the high response rates. Thorough recruitment of patients and controls, the high quality of asthma diagnosis based on clinical and lung function investigations, and the utilization of the inclusive medical and medication reimbursement records available in Finland ensure that we were able to identify and include a high proportion of new cases of adult-onset asthma and that all the asthma cases in our study were genuinely new and adult onset. The statistical analyses were adjusted for several environmental factors and other potential confounders. Our study is so far the largest one (477 cases and 842 controls) investigating the influence of parental asthma on adult-onset asthma and the only one using clinically defined asthma and considering the role of siblings' and children's asthma in this setting.

Our results strengthen the evidence that parental asthma is a strong determinant of adult-onset asthma and provide new evidence that the risk of adult-onset asthma is associated with the presence of asthma among siblings and the person's children. Our results also provide new evidence that the highest risk of adult-onset asthma is present among those with several categories of first-degree family members having asthma. From the clinical perspective, this means that asking the patient about the asthma of his or her siblings and children, in addition to parents, provides useful information on the probability of asthma.

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METHODS

This study was a population-based incident case-control study. The source population was adults 21 to 63 years of age living in a geographically defined administrative area of Pirkanmaa in South Finland. The population of the area was 440,913 in 1997.

Definition and selection of cases

We systematically recruited all new asthma cases reported during 1997 to 2000 in the whole Pirkanmaa Hospital District, at all health care facilities diagnosing asthma.^{E1,E2} As an additional route of case selection, the National Social Insurance Institution of Finland invited all patients whose reimbursement rights for asthma medication began during the study period, and who had not yet participated. The diagnostic criteria for asthma were (1) occurrence of at least 1 asthmalike symptom and (2) demonstration of significant reversibility in airways obstruction in lung function investigations (Table E1).^{E1,E3} To ensure that all the cases had asthma diagnosed for the first time at recruitment, the medical records of all cases were checked, and we selected as cases only those with no previously diagnosed asthma or long-term use of any asthma medication. At the Tampere University Hospital, cases were recruited at their first visit because of suspected asthma and the diagnosis was then verified in clinical examinations. A total of 521 cases participated (response rate 86%).

Selection of controls

The controls were randomly drawn from the source population, using the Population Register Center, which has full coverage of the population. The general eligibility criteria (living in Pirkanmaa, age 21–63 years) were applied for controls. Recruitment of controls took place at regular intervals during the study period by a letter or by phone. A total of 1016 controls participated (response rate 80%), and after excluding those with previous or current asthma ($n = 76$), those older than 63 years (6), and those with incomplete questionnaires (2), our study population included 932 controls.

Questionnaire

The study subjects answered a self-administered questionnaire that included 6 sections: 1. personal characteristics, 2. health information and family history of asthma and atopic diseases, 3. active smoking and second-hand smoke exposure, 4. occupation and work environment, 5. home environment, and 6. dietary questions.^{E1,E2,E4-E8} The information about family history of asthma was collected with the question “Do you have a close relative with asthma diagnosed by a doctor?” The study subjects were then asked to circle the number corresponding to mother and/or father if appropriate, and to fill in the blank spaces of the following statements: “I have altogether _ sisters and brothers, of whom _ have asthma.” and “I have _ children, of whom _ have asthma.” The subjects were asked to mark zero if they had no siblings or children, or if none of them had asthma. Those study subjects with missing information in all the questions concerning their first-degree relatives were excluded from this study, leaving 477 cases and 842 controls for the analyses. There were no statistically significant differences in the distribution of asthma or the basic characteristics between those who had answered these questions and those who had not. Collecting information on the heredity of asthma by questionnaire is a potential source of random or systematic error. However, the substantial national reimbursement of asthma medication leads to a high coverage of asthma diagnosis in the whole Finnish population and therefore supports our choice of collecting data on parental, siblings', and children's asthma by using a self-administered questionnaire.

Lung function measurements

The same diagnostic protocol was applied for all patients with suspicion of asthma. The details of lung function measurements have been described elsewhere.^{E1,E9} Shortly, spirometry and the bronchodilatation test were recorded with a pneumotachograph spirometer using a disposable flow transducer (Medikro 905; Medikro, Kuopio, Finland) according to the standards of the American Thoracic Society.^{E10} Presence of obstruction was defined on the basis of the reference values derived from the Finnish population.^{E11}

Statistical methods

Exposure OR with 95% CI derived from logistic regression models was used to quantify the relations between hereditary factors and the risk of adult-onset asthma. Sex, age, education (as an indicator of socioeconomic status), personal smoking, secondhand smoke exposure, any presence of pets in the home, occupational exposure to sensitizers, dusts, and/or fumes, mold problems at home or at work, and, when appropriate, the information about having siblings or children or the number of siblings or children were adjusted for as covariates. For 20 study subjects the information on the total number of siblings and for 10 subjects the information on the total number of children was missing, but the number of asthmatic siblings or children was given. These subjects were excluded from the analyses where the number of siblings and/or children was needed. To study the possible influence of siblings' or children's asthma on the risk of personal asthma, the ratio of asthmatic siblings or children to all siblings or children was calculated. These ratios were then divided into groups according to the median (calculated for those who had the ratio >0 ; for siblings, the median = 0.33; for children, the median = 0.50). Statistical analyses were performed by using SAS statistical package (SAS Institute, Inc, Cary, NC) version 9.3.

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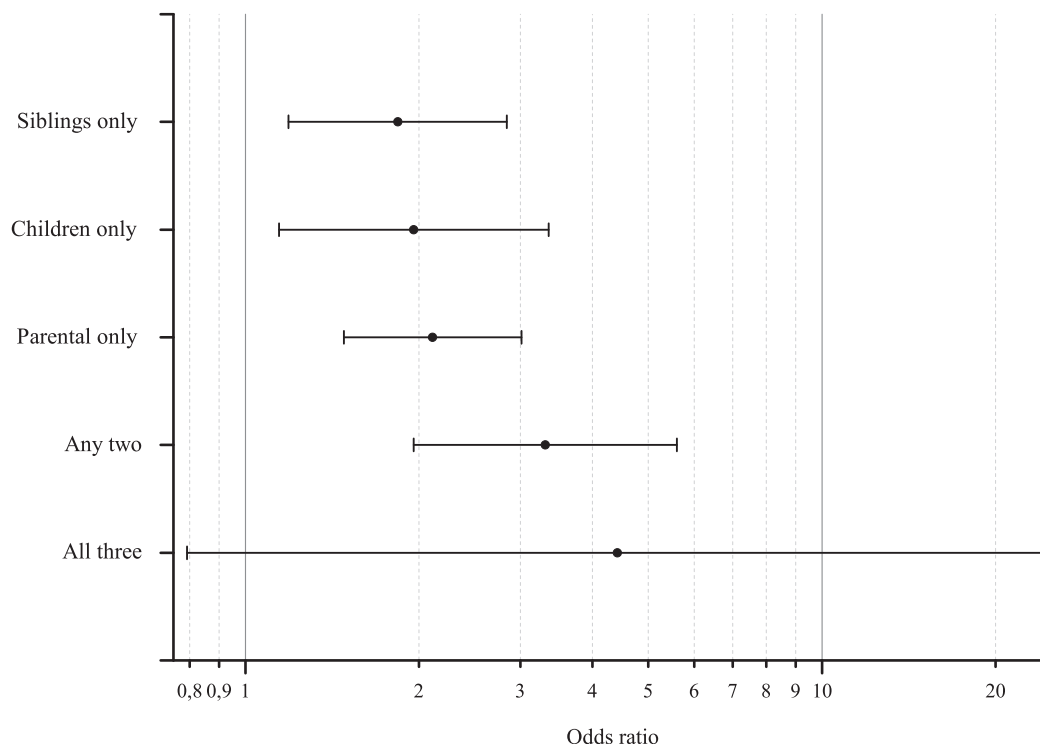


FIG E1. The risk of adult-onset asthma according to the types of first-degree relatives with asthma. OR with 95% CI derived from logistic regression models. Sex, age, education (as an indicator of socioeconomic status), personal smoking, secondhand smoke exposure, any presence of pets in the home, occupational exposure to sensitizers, dusts, and/or fumes, mold problems at home or at work, and the information about having siblings or children were adjusted for as covariates.

TABLE E1. Diagnostic criteria for asthma

1. Occurrence of at least 1 asthmalike symptom: prolonged cough, wheezing, attacks of or exercise-induced dyspnea, or nocturnal cough or wheezing
AND
2. Demonstration of significant reversibility in airways obstruction in lung function investigations:
Significant improvement in response to short-acting bronchodilating medication in a bronchodilator test after baseline spirometry or at the end of methacholine challenge. The criteria for significant changes were ^{E9} $FEV_1 \geq 15\%$, $FVC \geq 15\%$, $PEF \geq 23\%$.
AND/OR
$\geq 20\%$ daily variation* and/or $\geq 15\%$ improvement* in response to short-acting bronchodilating medication during at least 2 d in a 2-wk diurnal PEF monitoring
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-wk oral steroid treatment

FVC, Forced vital capacity; *PEF*, peak expiratory flow.

*Calculated according to the standard practice of the Tampere University Hospital: 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.