Upsala Journal of Medical Sciences

ISSN: 0300-9734 (Print) 2000-1967 (Online) Journal homepage: https://www.tandfonline.com/loi/iups20

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To cite this article: Monica Uddenfeldt, Christer Janson, Erik Lampa & Anna Rask-Andersen (2013) Sensitization to pets is a major determinant of persistent asthma and new asthma onset in Sweden, Upsala Journal of Medical Sciences, 118:2, 111-121, DOI: 10.3109/03009734.2012.752772

To link to this article: https://doi.org/10.3109/03009734.2012.752772

Upsala Journal of Medical Sciences. 2013; 118: 111–121

informa
healthcare

ORIGINAL ARTICLE

Sensitization to pets is a major determinant of persistent asthma and new asthma onset in Sweden

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Abstract

Introduction. Our knowledge about atopy as a longitudinal predictor of asthma is limited. The purpose of this study was to investigate the prognosis of asthma and risk factors for asthma onset, especially sensitization of specific allergens in a population sample.

Material and methods. A cohort responded to a respiratory questionnaire in 1990 and 2003. At baseline, 2,060 subjects who, in the screening questionnaire, reported respiratory symptoms and 482 controls were investigated with interviews, spirometry, and skin-prick test. A total of 721 asthmatics and 976 subjects without respiratory disease were clinically verified. At follow-up in 2003, 340 subjects with persistent asthma and 186 subjects with asthma remission were identified, while 76 subjects reported new asthma onset.

Results. Sensitization to pets and a high symptom score were significant determinants of persistent asthma (odds ratio (OR) 3.2 (95% CI 1.9–5.6) and 5.7 (2.5–13.3), respectively) and onset of asthma (OR 2.6 (1.1–6.0), and 1.7 (1.2–2.3)). A high self-reported responsiveness to airway irritants (OR 1.6 (1.1–2.2)), and more asthma medications (OR 2.0 (1.3–2.9)) were additional indicators of persistent asthma at the follow-up. Belonging to the older age group decreased the risk both of having persistent asthma and asthma onset.

Discussion. Asthmatics sensitized to pets have a more severe outcome than asthmatics not sensitized to pets. Sensitization to pets was also a strong predictor for onset of asthma. Special attention should be given to asthmatics who report having severe symptoms and problems with airway irritants as such patients are more likely to have persistent problems.

Key words: *Allergens, allergy tests, asthma, longitudinal study, prognosis, skin-prick test*

Introduction

The prevalence of asthma has been increasing in Sweden and a number of other countries during the last decades (1,2), but a study from Sweden might indicate that a plateau has been reached (3). During the last few years there has been a growing interest in dividing asthma according to phenotype as studies have shown distinct differences between various asthma subtypes (4). Thus, different strategies have been developed to classify the patients into different phenotypes. Rackemann was the first to report a distinction of what is now called atopic/non-atopic asthma or allergic/non-allergic asthma (5). Rhinitis, conjunctivitis, and eczema are more frequent in atopic asthmatics as well as in those with a family history of asthma, eczema, and rhinitis, emphasizing that atopy and related diseases are traits inherited together (6). Some studies have demonstrated immunological similarities between atopic and non-atopic asthma, while others find that atopic and non-atopic asthma are two distinct phenotypes (7–9).

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(Received 18 October 2012; revised 18 November 2012; accepted 21 November 2012)

ISSN 0300-9734 print/ISSN 2000-1967 online
DOI: 10.3109/03009734.2012.752772

The importance of atopy as the key factor for initiation and maintenance of clinical asthma is most widely accepted for childhood asthma. Asthmatic patients without atopy are usually older, show negative skin-prick tests, and lack evidence of IgE antibodies specific to common environmental allergens. A Danish study found that the rate of decline in lung function during a 10-year follow-up study was greater in patients with non-atopic asthma compared to those with atopic asthma (10). In a study from the European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA), a number of findings suggested that atopy was less important as a predictor of the development of severe asthma. Thus the group with severe asthma had lower total serum IgE, fewer positive skin-prick tests, and radioallergosorbent tests to common allergens compared to subjects with controlled asthma. Also, an inverse relationship to a family history of atopy among the severe asthmatics was observed. Likewise, exacerbations were more frequent in the autumn rather than during the pollen season (11).

The purpose of the present study was to investigate the outcome of asthma in a population sample especially related to atopy and sensitization to specific allergens. A secondary aim was to investigate the relationship between atopic sensitization and onset of adult asthma.

Material and methods

Study area

This was a longitudinal study with an epidemiological design including a baseline measure in 1990 (12) and a follow-up in 2003 (2). The study area is located in central Sweden and has an area approximately the size of Denmark.

Study design and sample

In 1990, postal questionnaires were distributed to all individuals born in 1974 and to a random sample of individuals born 1951–1960 and 1921–1931 in the counties of Gästrikland and Jämtland in the central part of Sweden. Subjects not responding to the first mailing received two reminders. A total of 11,294 subjects (response rate 90%) answered the screening questionnaire on respiratory symptoms. In a second phase, all subjects who reported a history of asthma, chronic bronchitis, or respiratory symptoms (n = 2,538), and a random sample of 600 subjects without a history of respiratory diseases and respiratory symptoms, were invited to interview, spirometry, and allergy testing (13). The participation rate was 81%. After the clinical investigation, 721 subjects were diagnosed with asthma and 976 without asthma or any other respiratory disease. Of those, 667 and 912, respectively, remained in the closed cohort at follow-up in 2003 (Figure 1).

In 2003, the same respiratory questionnaire used in 1990 was sent out to the 667 subjects with clinically verified asthma in 1990 as well as to the 912 subjects without asthma or other respiratory disease in 1990. The response rates were 79 and 58%, respectively.

Measurements

Questionnaire on respiratory symptoms

The postal questionnaire in 1990 was based on a questionnaire which was used in the OLIN-studies in northern Sweden (14). The questionnaire consisted of 22 items, including: attacks of dyspnoea, shortness of breath, or breathlessness; wheezing in the chest; prolonged productive cough; use of anti-asthmatic medication; physician's diagnosis of asthma, chronic bronchitis, or emphysema.

The first part of the 2003 questionnaire with the 22 items was identical to that in 1990, including questions on respiratory symptoms, asthma, hay-fever, heredity, and smoking habits. The second part of the questionnaire 2003 included 92 new items regarding, for example, weight, height, physical activity, dietary factors, gastro-oesophageal reflux, sleep disorders, snoring, occupational exposure, and indoor environment (as previously used in the European Community Respiratory Health Survey).

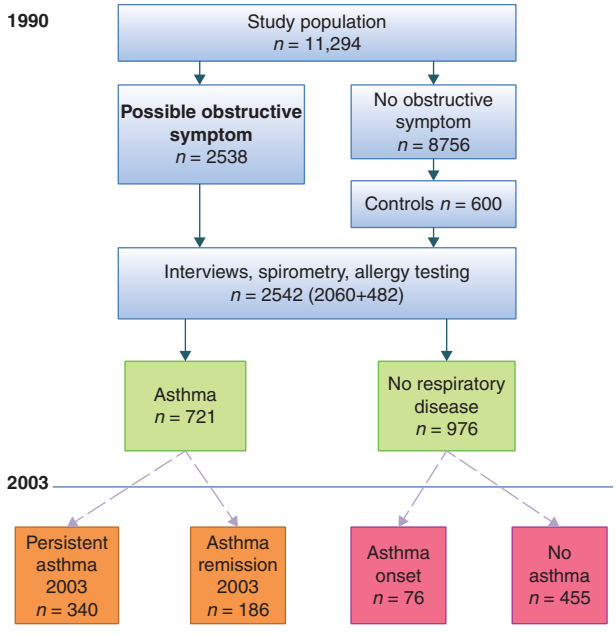

Figure 1. Study population and design of the study.

Clinical measurements

The clinical measurements consisted of spirometry, a skin-prick test, recording of peak expiratory flow (PEF) variability, and a methacholine challenge. Lung function was tested with a pneumotachograph (Vitalograph Alpha, London, UK). Vital capacity (VC) and forced expiratory volume in 1 second (FEV_1) were measured. This study adhered to recommendations for spirometry testing by the American Thoracic Society. A skin-prick test was performed using a Phazet® lancet (Pharmacia Diagnostics, Uppsala, Sweden), which was pre-coated with standardized extracts of 10 common allergens. Lancets with allergen were applied on the inside of the forearm.

When investigated, all subjects were asked to record PEF for 1 week with a mini-Wright peak flow meter as described by Higgins (15). All days with at least three recordings were identified, and the amplitude in per cent of the mean of the day was calculated. Subjects with a history suggestive but not diagnostic of asthma were invited to perform a methacholine inhalation. The method has been described elsewhere (13).

Definitions

Asthma diagnosis. The protocol to confirm asthma involved two visits. The first visit involved an interview, pre- and post-bronchodilator spirometry, and instructions to record PEF for 1 week after the examination with a mini-Wright peak flow meter. Asthma was confirmed and no further testing was required if all of the following symptoms and findings were present in combination with a best FEV_1 >80%: repeated attacks of wheezing or shortness of breath in the last year, identified exogenous agents provoking wheeze or shortness of breath, and complete recovery between attacks. If symptoms and findings were inconclusive, and the subject showed an improvement in FEV_1 of >300 mL or 15% after bronchodilator was given, then asthma was confirmed. If spirometry was negative the subject returned for a bronchial challenge test with methacholine at visit 2. If the methacholine test was positive (i.e. revealed a provocative concentration of methacholine causing a 20% fall in FEV_1 (PC20) of <4), then asthma was confirmed. If PC20 was 4–8 and PEF >20% (amplitude % mean) in 3 of 7 days, then asthma was confirmed.

Asthma remission and persistent asthma. The asthmatics were divided into two groups based on the answers from the follow-up during 2003. The group 'asthma remission' was identified by no asthma attacks during the last year, or current asthma medication in 2003. The group 'persistent asthma' comprised asthmatics who reported having had asthma attacks during the previous year or currently took asthma medication.

Asthma onset. In the group of subjects without asthma at baseline, asthma onset was defined according to the answers to four questions in the questionnaire in the follow-up in 2003. These questions were: 'Do you have or have you had asthma?', 'Have you ever been diagnosed with asthma by a doctor?', 'Do you use asthma medication?', and 'Do you have or have you had symptoms of asthma (attack of difficulty of breathing or breathlessness, with or without cough, with or without wheezing in the chest)?' The respondents were considered as having an onset of asthma if they answered 'yes' to one or more of these questions.

Determinants

From the investigation in 1990 with respiratory questionnaires and interviews by a nurse who had special training in questionnaires and other study-related issues, the following questions were chosen in order to estimate determinants of asthma. The process of choosing these variables was based on discussions in the research team and also on earlier research and clinical experience.

Smoking habits. Smoking habits were classified into three categories–non-smokers, ex-smokers, and smokers.

Positive skin-prick tests. A mean weal diameter of ≥3 mm was regarded a positive response. Skin test results with a mean diameter of the negative control more than 2 mm, or with a negative histamine as positive control, were excluded from the analyses. The reactions to the allergens were grouped into four categories – pets (cat, dog, and horse), house dust mites (*Dermatophagoides pteronyssinus* and *D. farinae*), moulds (*Alternaria tenuis* and *Cladosporium herbarum*), and pollen (birch, grass, and mugwort). Atopy was defined as the presence of one or more positive skin tests to these common allergens.

Self-reported responsiveness to airway irritants. Self-reported responsiveness to airway irritants were classified into six groups according to the answers to questions on the following five topics: 1) breathlessness on exhaustion in cold air during the winter; wheezing or severe cough after exposure to 2) dust, 3) cigarette smoke, 4) vehicle exhaust/air pollution, or 5) strong smells. Subjects with no such symptoms

Table I. Characteristics of subjects with improved asthma 2003 and persistent asthma 2003.

Determinants		Improved asthma 2003 $n = 186$ Per cent (n)	Persistent asthma 2003 $n = 340$ Per cent (n)	P value
Sex	Males	37% (68)	40% (135)	$P = 0.478$
Age groups	16-year-olds	22% (40)	31% (107)	$P < 0.001$
	30–39-year-olds	39% (72)	45% (154)	
	60–69-year-olds	40% (74)	23% (79)	
Smoking habits	Non-smokers	50% (92)	57% (192)	$P = 0.020$
	Ex-smokers	19% (35)	23% (78)	
	Smokers	31% (57)	20% (68)	
Positive skin-prick tests	All allergens	40% (72)	64% (217)	$P < 0.001$
	Pets	20% (36)	49% (166)	$P < 0.001$
	Cat	16% (29)	38% (130)	$P < 0.001$
	Dog	11% (21)	36% (123)	$P < 0.001$
	Horse	7% (13)	24% (81)	$P < 0.001$
	Mites	11% (21)	15% (52)	$P = 0.208$
	D. pteronyssinus	11% (21)	15% (52)	$P = 0.208$
	D. farinae	8% (14)	12% (42)	$P = 0.056$
	Moulds	5% (10)	10% (34)	$P = 0.068$
	Alternaria	2% (4)	4% (12)	$P = 0.381$
	Cladosporium	4% (8)	9% (30)	$P = 0.381$
	Pollen	28% (52)	45% (153)	$P < 0.001$
	Birch	19% (36)	36% (122)	$P < 0.001$
	Grass	18% (33)	34% (116)	$P < 0.001$
	Mugwort	5% (10)	10% (34)	$P = 0.068$
Spirometry	FEV_1 mean (SD)	100 (13)	97 (15)	$P = 0.043$
Self-reported responsiveness to airway irritants	None	14% (26)	6% (20)	$P = 0.011$
	One irritant	21% (38)	16% (55)	
	Two irritants	24% (45)	23% (79)	
	Three irritants	21% (39)	27% (93)	
	Four irritants	14% (26)	19% (64)	
	Five irritants	6% (11)	8% (28)	
Symptoms score	No symptoms	12% (22)	6% (20)	$P = 0.003$
	Wheeze during last year	19% (35)	13% (45)	
	Nightly sympt./Asthma attacks	63% (117)	67% (229)	
	Breathlessness on most days	6% (12)	14% (46)	
Asthma medication score	No medication	74% (134)	40% (132)	$P < 0.001$
	Low doses	9% (16)	20% (65)	
	Moderate doses	9% (17)	18% (58)	
	High doses	6% (10)	16% (52)	
	Oral steroids	2% (4)	6% (20)	

were graded into group 1, while subjects answering yes to all five questions were placed in the sixth group.

Respiratory symptom score. The severity of obstructive symptoms in 1990 was classified into four groups: no symptoms, wheezing during the last year (Mild), nightly symptoms such as wheezing of breathlessness or asthma attacks during the last year (Moderate), and breathlessness during most days of the week (Severe).

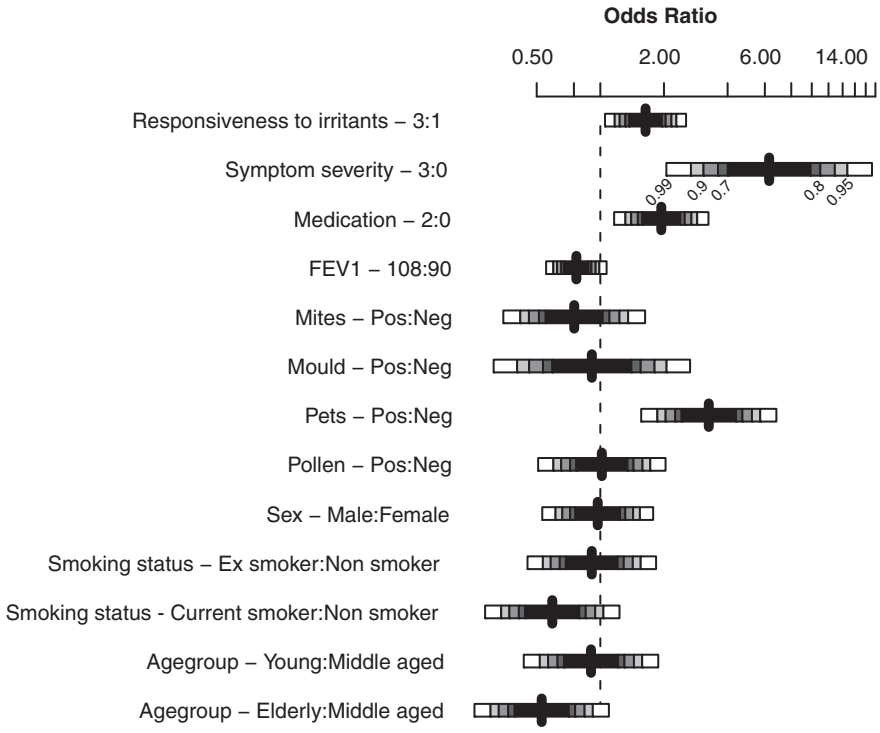

Figure 2. Determinants of persistent asthma 2003 in subjects with clinically verified asthma 1990 analysed with multiple logistic regressions. Results shown on a logarithmic scale as ORs (odds ratios) with different levels of confidence intervals with figures and shades of grey (light grey 95% CI, see the determinant 'Symptom severity'). The values of the independent determinants that are compared are indicated in the figure (interquartile distance for FEV_1).

Asthma medication. The asthma medication was categorized into four groups: 1) no treatment; 2) bronchodilators on demand; 3) regular use of inhalational steroids; and 4) medications, including oral steroids.

Statistical analysis

Associations between the determinants and the outcomes of 1) persistent asthma and 2) incident asthma after 13 years were estimated using two logistic regression models, henceforth labelled models A and B, respectively. To avoid problems with over-fitting, a general rule is that the number of events (or non-events, whichever is the least frequent) per estimated regression coefficient, i.e. degrees of freedom, should be at least 15 (17). With the FEV_1 effect assumed to be linear, the number of non-events per degree of freedom in model A was 11.3, and the number of events per degree of freedom in model B was 6.1. Thus some over-fitting in both models can be expected.

The patterns of missing values in our data were first explored by cluster analysis. To gain further insight into which determinants might predict missing outcome values, we fitted logistic regression models to predict missingness of the outcome variables in model A and B. Missing values in the data can bias the results, and by using single imputation one usually underestimates the standard error by not taking into account the added variability due to imputation. We used multiple imputations of the missing values, using the outcome and all determinants to impute missing values, and fitted the models both with, and without, imputation for comparison.

To gauge the relative importance of the determinants, we calculated the partial Wald chi-square statistic minus the determinant degrees of freedom (16). A higher value implies more predictive power. We calculated the *c*-index (i.e. the area under the ROC curve) for both models as a measure of how concordant the predicted probabilities and outcomes are. We are aware that the values are likely to be overoptimistic due to fitting and interpreting the models on the same data. The amount of over-fitting in the models was calculated according to Harrell (17). All analyses were performed using R version 2.10.0.

Ethics approval

The study was approved by the Ethics Committee at the University of Umeå (§222, 1989-12-12) and the Ethics Committee, Faculty of Medicine, Uppsala (Dnr. 01–313).

Table II. Independent determinants of persistent asthma and onset of asthma. The results are expressed as adjusted odds ratios with a 95% confidence interval (OR (95% CI)).

	Persistent asthma OR (95% CI)	New asthma OR (95% CI)
Males	1.0 (0.6–1.5)	1.0 (0.6–1.7)
Age groups		
16-year-olds	1.0 (0.5–1.7)	1.6 (0.9–3.1)
30–39-year-olds	1	1
60–69-year-olds	0.5 (0.3–0.9)	
Smoking habits		
Non-smokers	1	1
Ex-smokers	1.0 (0.5–1.7)	1.0 (0.5–1.9)
Smokers	0.6 (0.3–1.1)	1.0 (0.5–2.1)
Positive skin-prick tests		
Pets	3.2 (1.9–5.6)	2.6 (1.1–6.0)
Mites	0.8 (0.4–1.5)	0.6 (0.3–1.3)
Moulds	0.9 (0.4–2.1)	2.1 (0.5–8.8)
Pollen	1.0 (0.6–1.7)	1.3 (0.7–2.4)
FEV_1	0.8 (0.6–1.0)	1.0 (0.7–1.4)
Response irritants	1.6 (1.1–2.2)	1.2 (1.0–1.6)
Symptoms score	5.7 (2.5–13.3)	1.7 (1.2–2.3)
Asthma medication	2.0 (1.3–2.9)	0.7 (0.3–1.3)

Results

Among the subjects with clinically verified asthma in 1990, 340 subjects were defined as having persistent asthma and 186 subjects as having asthma remission in 2003. Among the subjects without asthma in 1990, 76 subjects were defined as having an onset of asthma in 2003, while 455 subjects remained free of asthma.

The characteristics of the 305 subjects with persistent asthma and 155 subjects with asthma remission are shown in Table I. The univariate analysis shows that young adults reported persistent asthma significantly more often than the middle-aged and the elderly. Subjects with persistent asthma reported significantly higher responsiveness to airway irritants, higher symptom score, and more asthma medications than subjects with asthma remission. The skin-prick tests were significantly more often positive to pets and pollen in this group with persistent asthma. Cat, dog, horse, birch, and grass were the allergens of highest significance ($P < 0.001$). Nineteen per cent of the respondents reported having a cat at home in 1990, and 22% had a dog. No significant difference regarding pets was found between subjects with persistent asthma and subjects in the asthma remission group.

Subjects reporting an onset of asthma reported more responsiveness to airway irritants at baseline. The skin-prick tests performed in 1990 were significantly more often positive to pets, moulds, and pollen. No significant difference regarding pet keeping was found between subjects reporting asthma onset compared to subjects without asthma onset.

The multiple logistic regressions showed that the significant determinants of persistent asthma were positive skin-prick test to pets (OR 3.2 (95% CI 1.9–5.6)), higher symptom score (OR 5.7 (95% CI 2.5–13.3)), a high self-reported responsiveness to airway irritants (OR 1.6 (95% CI 1.1–2.2)), and more asthma medications (OR 2.0 (95% CI 1.3–2.9)) (Figure 2 and Table II). Belonging to the older age group decreased the risk of having persistent asthma (OR 0.5 (95% CI 0.3–0.9)). Sex, smoking habits, and decreased FEV_1 at baseline were not significant determinants for persistent asthma.

The characteristics of the 76 subjects who reported asthma onset during follow-up and the 455 subjects with no self-reported asthma are presented in Table III.

The significant determinants of asthma onset were positive skin-prick test to pets (OR 2.6 (95% CI 1.1–6.0)) and high symptom score (OR 1.7 (95% CI 1.2–2.3)) (Table II and Figure 3). Young adults had a higher risk for asthma onset compared to the elderly. The relative importance of the determinants is shown in Figure 4 (persistent asthma) and Figure 5 (asthma onset). Sensitization to pets was the most important determinant for both persistent asthma and onset of asthma, followed by symptom score and medication for persistent asthma, and age group and symptom score for new asthma onset.

Missing values were most frequent in the outcome variables (21% in model A, persistent asthma, and 42% in model B, incident asthma). Other variables combined for missing values were 8% of all cases in model A and 3% in model B. For model A, the probability of a missing outcome increased with increasing values of FEV_1, smoking, younger age, male sex, and sensitization to mites. For model B, the probability of a missing outcome increased with increasing symptom severity, younger age, sensitization to mites, pets, and pollen, and, to a lesser extent, male sex and increasing values of FEV_1.

Discussion

In this longitudinal study sensitization to pets and a higher reported responsiveness to airway irritants were significant determinants of both persistent asthma and onset of asthma. Higher symptom and medication scores at baseline were additional risk factors for persistent asthma at the follow-up.

Table III. Characteristics of subjects without asthma 1990 with no asthma 2003 and new onset asthma 2003. Presented as per cent (number of non-missing observations) for categorical variables and 25th percentile/median/75th percentile for continuous variables.

Determinants		No asthma 2003) (n = 455) Per cent (n)	New onset asthma 2003) (n = 76) Per cent (n)	P value
Sex	Males	45% (206)	42% (32)	$P = 0.607$
Age groups	16-year-olds	24% (111)	38% (29)	$P = 0.01$
	30–39-year-olds	46% (209)	46% (35)	
	60–69-year-olds	30% (135)	16% (12)	
Smoking habits	Non-smokers	62% (284)	67% (51)	$P = 0.606$
	Ex-smokers	21% (94)	16% (12)	
	Smokers	17% (77)	17% (13)	
Positive skin-prick tests	All allergens	26% (104)	39% (26)	$P = 0.036$
	Pets	9% (40)	27% (20)	$P < 0.001$
	Cat	5.6% (22)	17.9% (12)	$P < 0.001$
	Dog	4.6% (18)	11.9% (8)	$P = 0.015$
	Horse	3% (10)	10% (7)	$P < 0.001$
	Mites	11% (48)	9% (7)	$P = 0.727$
	D. pteronyssinus	9% (37)	7% (5)	$P = 0.616$
	D. farinae	6% (25)	3% (2)	$P = 0.281$
	Moulds	2% (9)	7% (5)	$P = 0.020$
	Alternaria	1% (3)	4% (3)	$P = 0.013$
	Cladosporium	1% (5)	4% (3)	$P = 0.062$
	Pollen	16% (74)	29% (22)	$P = 0.008$
	Birch	10.1% (40)	16.4% (11)	$P = 0.129$
	Grass	10.6% (42)	13 (19.4%)	$P = 0.040$
	Mugwort	4.1% (16)	6.0%(4)	$P = 0.475$
Spirometry	FEV_1 per cent of predicted	94/103/112	95/104/110	$P = 0.942$
Self-reported responsiveness to airway irritants	None	59% (268)	34% (26)	$P = 0.002$
	Two irritants	23% (103)	38% (29)	
	Three irritants	11% (51)	20% (15)	
	Four irritants	5% (22)	4% (3)	
	Five irritants	2% (8)	4% (3)	
	One irritant	1% (3)	0% (0)	
Symptoms score	No symptoms	80% (365)	58% (44)	$P < 0.001$
	Wheeze during last year	15% (66)	37% (28)	
	Nightly symptoms/ Asthma attacks	5% (23)	5% (4)	
	Breathlessness on most days	0% (1)	0% (0)	

The results of this study indicate that sensitization to pets was related both to persistence of asthma and increased risk of onset of asthma. Plaschke et al. reported that cats and dogs, but not mites, were the sensitizing allergens most closely associated with asthma and bronchial hyperresponsiveness in Swedish adults (18). In a subsequent study, the same research group also found that pet sensitization, but not pollen or mite sensitization, was a risk factor for onset of asthma (19). The lack of association between asthma and sensitization to mite and pollen was also confirmed in the present study. Because of the cold winter climate in this region, exposure to mite is low and pollen is only a seasonal allergen. We did not find that asthmatics had more pets at home. Nineteen per cent reported cats in the home in

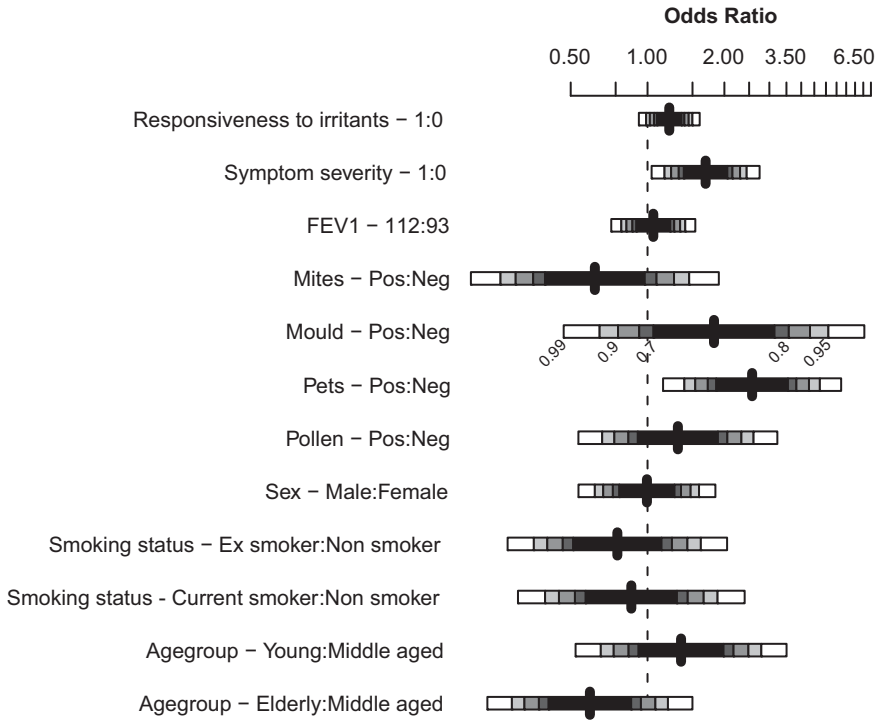

Figure 3. Determinants of asthma onset 2003 in subjects without asthma in 1990 analysed with multiple logistic regressions. Results shown on a logarithmic scale as OR (odds ratio) with different levels of confidence intervals with figures and shades of grey (light grey 95% CI, see the determinant 'Mould'). The values of the independent determinants that are compared are indicated in the figure (interquartile distance for FEV_1).

1990 and 22% had a dog, but there were no significant differences between asthmatics and non-asthmatics. Exposure to pets, mostly to cat and dog, is very common in Sweden (20).

Cat and dog allergens can be found in virtually all homes, but, not surprisingly, homes with pets contain much higher levels of the allergens than homes without pets (21). Furred pet allergens are also found in other settings, such as schools and other public buildings (22), and are passively transferred from one environment to another (23). The combination of widespread exposure to pet allergens and high prevalence of allergic sensitization to pet allergens suggests that a substantial proportion of patients with asthma are at risk for cat or dog allergen-induced asthma symptoms. In fact, several studies have directly linked animal allergen exposure to poorer asthma outcomes among animal-sensitized patients with asthma (23,24). However, several reports have indicated that living with a pet reduces the risk for becoming sensitized to that pet, but having a pet in the home results in exposure to more than just allergens. In a recent review, inconsistent results were found for cat ownership, with some studies suggesting an increase in risk and others a decreased risk among cat owners (25). For dogs, results were more consistent, generally suggesting that owning a dog has no effect or may even be protective against the development of specific sensitization to dog and allergic sensitization in general.

Bronchial hyperresponsiveness has been identified as a risk factor in the development and outcome of asthma (26,27). In our study methacholine challenge was only carried out in a subset of the study population. Instead, we used self-reported responsiveness to airway irritants as a surrogate for methacholine challenge. The results did show that a high self-reported responsiveness to irritants was a significant determinant of persistent asthma. Self-reported responsiveness to airway irritants was not a determinant for new asthma onset. This could, at least to some extent, be explained by the fact that some subjects could have been suffering from sensory hyperreactivity: a syndrome described in patients with pronounced airway sensitivity to environmental irritants like odorous chemicals and scents, but without objective signs of asthma (bronchial obstruction) or allergy, but with an increased cough sensitivity to inhaled capsaicin (28).

Our results indicate that atopic subjects with asthma are less likely to remit than non-atopic subjects with asthma. These results are in accordance

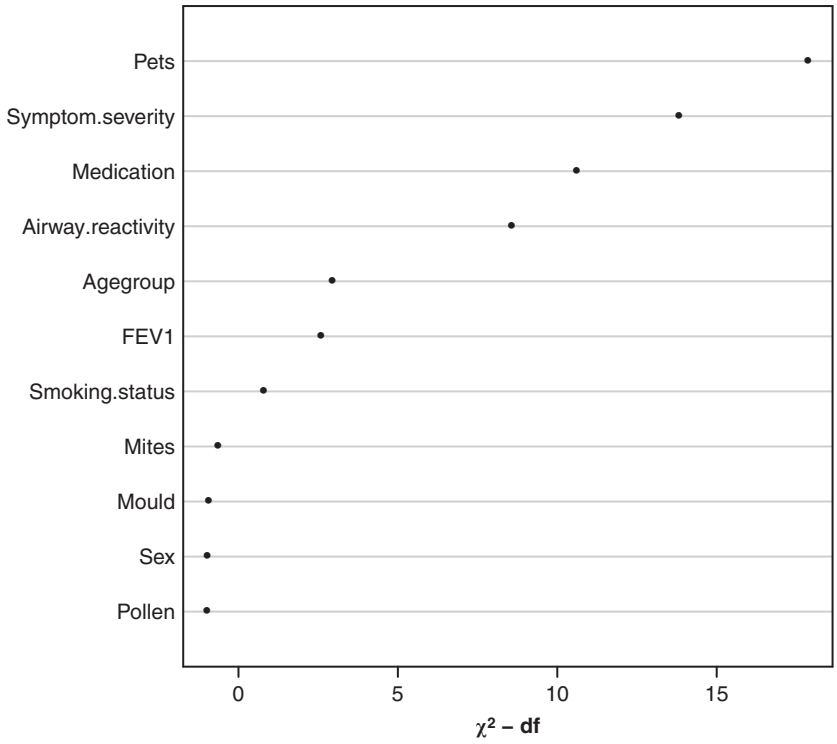

Figure 4. Importance of the different determinants in predicting persistent asthma after 13 years as judged by the partial Wald chi-square minus degree of freedom. The higher value on the *x*-axis, the more the determinant contributes to the prediction.

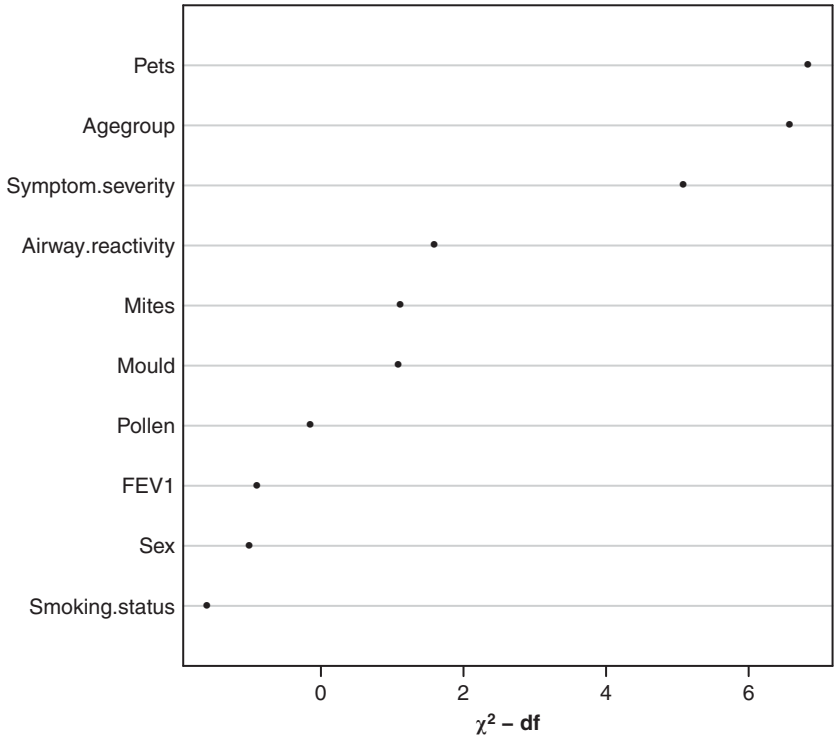

Figure 5. Importance of the different determinants in predicting incident asthma after 13 years as judged by the partial Wald chi-square minus degree of freedom. The higher value on the *x*-axis, the more the determinant contributes to the prediction.

to the results of a longitudinal study on Swedish children (29). Greater reversibility in FEV_1 has been reported in patients with atopic asthma than in patients with non-atopic asthma in a Danish study (10). In the same study, non-atopic asthmatics had a steeper decline in FEV_1 during a 10-year follow-up. In a French study, non-allergic asthma was more severe than allergic asthma (30). Adult onset of asthma and absence of atopy in male patients were associated with persistent airflow limitation in a Dutch study (31). The discrepancy between these studies and the present study regarding the prognosis of atopic and non-atopic asthma may reflect differences in the selection of the asthma population. The previous studies were based on asthmatics referred to secondary care at expert clinics, whereas the present study was population-based. Also, in the ENFUMOSA study, all patients were recruited through hospital out-patient departments and not through an epidemiological survey of representative populations in each country, as emphasized by the authors (11). It is possible that the pattern of referral differed between patients with atopic asthma and non-atopic asthma. The patients with a history of allergy might have been referred to an allergy clinic to confirm the allergy, while patients with non-allergic asthma might have been referred if their asthma was more severe or more difficult to treat. Thus, a population-based study on the difference in outcome between atopic and non-atopic asthmatics could provide better information on the natural history of asthma than studies with selected patients attending clinics.

A weakness of this study is that weight was not measured at baseline. In a recent cross-sectional study of over 80,000 Canadians, the association between increased BMI and asthma was stronger among non-allergic adults compared with allergic adults, especially in women (32). Other studies have confirmed that non-allergic asthma is more common in women (30) and that there is a stronger relationship between obesity and asthma in women than in men. However, we could not confirm any sex differences in the relationship between obesity and asthma in a recently published analysis of our study where we used BMI at follow-up (2).

In conclusion, the findings of this longitudinal cohort study show that asthmatics sensitized to pets have a more severe outcome than asthmatics not sensitized to pets. Sensitization to pets was also a strong predictor for onset of asthma. Our study also indicates that special attention should be given to asthmatics who report having problems with a high number of airway irritants as such patients are more likely to suffer from persistent problems.

Acknowledgements

This study was supported financially by the Swedish Heart and Lung Foundation, the Gävleborg County Council Research Fund, and the Swedish Association against Asthma and Allergy.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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