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Multi-symptom asthma as an indication of disease severity in epidemiology

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INTRODUCTION

Only few studies have attempted to identify severe asthma in different populations, which explains why the prevalence of more severe disease is largely unknown [1-4]. Clinical studies suggest that severe asthma is more common among women [1, 2] and compared with asthma in general, a greater proportion have presence of neutrophilic inflammation [2, 3]. Occupational exposure has also been shown to be associated with more severe asthma [4]. Asthma with more pronounced severity greatly affects daily life with an impaired quality of life, more frequent premature retirements and an increased risk of hospitalisation and death [1, 5, 6]. Severe asthma also causes the most significant economical burden of asthma, despite representing a minority of those with asthma [7, 8].

Studies of severe asthma have primarily been performed in clinical cohorts, as defining severe asthma in population studies has been difficult. Therefore, severe asthma has been sparsely studied in population cohorts [9]. Asthma with multiple symptoms, despite the concurrent use of asthma medication, is more readily defined in population studies and could potentially be used as a severity index. The West Sweden Asthma Study (WSAS) presents an opportunity to study severe asthma in a population sample. The WSAS was initiated in 2008 and provides a possibility to study extensive aspects of asthma epidemiology, including severity [10-12]. The study includes a postal questionnaire to a large sample of the general population in West Sweden, and clinical investigations of a randomly selected subsample of those with asthma.

The present study aims to determine the prevalence and risk factors of asthma with multiple respiratory symptoms despite the use of asthma medication. A secondary aim was to determine whether the definition of multi-symptom asthma is reflected by clinical manifestations of more severe disease.

MATERIAL AND METHODS

Study population and participation

The study population has previously been described [10]. In 2008, a questionnaire was mailed to 30 000 randomly selected subjects aged 16-75 years, living in the region of West Gothia, Sweden; 15 000 subjects lived in metropolitan Gothenburg and 15 000 in the remaining West Gothia. The population of the area was one-sixth of the Swedish population in 2007. As some subjects could not be traced the study sample consisted of 29 218 subjects of whom 18 087 subjects responded (62%). A non-responder study has been performed [11].

Questionnaire

The questionnaire consisted of three parts; the Swedish Obstructive Lung Diseases in Northern Sweden (OLIN) questionnaire, questions on occupation, retirement and exposure related symptoms and the Swedish version of the Global Allergy and Asthma European Network (GA^2LEN) questionnaire [13, 14]. The questionnaire included questions on asthma, chronic bronchitis/COPD/emphysema, rhinitis, eczema, respiratory symptoms, use of asthma medication and possible determinants of disease, such as smoking habits, occupation, airborne occupational exposures and family history of airway diseases.

Clinical examinations

Clinical examinations were performed in a subsample of the questionnaire respondents. Examinations included skin-prick tests (SPT), height and weight measurements, fraction of exhaled nitric oxide (FENO) at a flow rate of 50 ml/sec, spirometry and methacholine challenge. In total, 371 non-asthmatics and 472 asthmatics were clinically investigated. The skin prick test (SPT) was performed using a standard panel of 11 inhalant allergens (ALK, Hørsholm, Denmark), see online depository. A mean wheal diameter equal or greater than the positive control was considered as a positive response. Spirometry was performed (Masterscope, Jaeger, Höchberg, Germany) and the percentage of predicted FEV_1 was calculated. The methacholine challenge was performed using the Spira equipment and followed a shortened protocol with a highest administered cumulative dose of 1.96 mg. The formula used to calculate PD20 can be found in the online depository. The asthmatics that underwent clinical examinations were classified according the Global Initiative for Asthma (GINA) 2006 classification using frequency of symptoms and lung function [15]. The definitions used for the GINA classification are given in the online depository.

Definition of multi-symptom asthma

Subjects reporting *physician-diagnosed asthma* and *asthma medication* and *attacks of shortness of breath* and *recurrent wheeze* and at least one out of *dyspnoea, breathlessness – exertion, breathlessness – cold*, and *breathlessness – exertion in cold* were considered as multi-symptom asthmatics. For the purpose of this paper, all subjects reporting *physician-diagnosed asthma* but without multi-symptom asthma, are referred to as having "other asthma". Non-asthmatics did not report physician-diagnosed asthma. The rationale and hypothesis behind the definition of multi-symptom asthma and definitions about diseases, symptoms and possible determinants of disease are given in the online depository.

Analyses

The prevalence and risk factor calculations were based on all 18 087 questionnaire responders. Presented clinical data was obtained from a subsample of 843 subjects. Statistical analyses were performed using SPSS version 16.0. Comparisons of proportions were tested using chi-square tests, p-values were calculated using Fischer's exact test and the Mantel-Haenszel's test for trend was used where appropriate. T-tests were used to compare means in two groups. A p-value of <0.05 was regarded as statistically significant. Covariates used in the analyses included family history of asthma and/or allergy, rural/farm childhood, smoking habits, age, sex, area of residence, occupational exposure and allergic rhinitis. Allergic rhinitis was used as a surrogate variable for atopy. In the logistic regression models two of the variables, family history of asthma and family history of allergy, were combined. Three logistic regression models were performed. First, the OR for multi-symptom asthma was calculated using non-asthma as reference group; second, other asthma was compared with non-asthma and third, multi-symptom asthma was compared with other asthma. In addition, a multinomial regression model was created incorporating all three groups. The results can be seen in the online depository. The attributable fraction (AF), i.e. the proportion of cases caused by a specific factor, was calculated according to the formula ((RR-1) / RR) x p, where RR is the Risk Ratio and p is the proportion of exposed cases [16]. RR was calculated according to the formula (a/(a+b)) / (c/(c+d)) where a is the number of subjects with multi-symptom asthma exposed to the factor, b is the number of subjects without asthma exposed to the factor, c is the number of subjects with multi-symptom asthma not exposed to the factor and d is the number of subjects without asthma not exposed to the factor.

RESULTS

Prevalence and symptoms of multi-symptom asthma

Multi-symptom asthma was detected in 2.0% of the population. No significant differences were found by age, while it was significantly more common among women compared to men (2.4 vs. 1.5%, $p<0.001$). Subjects with multi-symptom asthma comprise 24.4% of subjects with physician-diagnosed asthma. All investigated symptoms were more common among multi-symptom asthmatics compared to non-asthmatics while all symptoms, except allergic rhinitis, were more common compared to subjects with other asthma (Table 1).

Clinical characteristics

Lung function, expressed as FEV_1% of predicted, was lower in both multi-symptom asthma and other asthma vs. healthy controls and lower in multi-symptom asthma vs. other asthma (Table 2). Of multi-symptom asthmatics, 82.9% reacted with >20% decrease in FEV_1 to cumulative doses of methacholine up to 1.96 mg compared to 58.7% of those with other asthma ($p=0.004$) and 40.1% of the non-asthmatics ($p<0.001$) (Table 2, Figure 1). When this highly positive bronchial challenge is used as a physiological diagnosis of asthma, multi-symptom asthma as test yields a positive predictive value of 83%, a specificity of 94%, while sensitivity is lower (34%) as also better controlled asthma with fewer symptoms often react on relatively low doses of methacholine. Subjects with multi-symptom asthma and other asthma had a higher number of positive SPTs compared to non-asthmatics, but there were no differences between the two groups of asthma (Table 2). There were no differences in the number of positive SPTs between multi-symptom asthmatics and other asthmatics, nor were there any differences which allergens they reacted to. Obesity was more common in multi-symptom asthma compared to the other two groups. FENO increased with increased asthma severity. Morbidity variables, particularly emergency unit visits and asthma exacerbations were considerably more common among multi-symptom asthma compared to other asthma (Table 2). According to the GINA 2006 classification, 59.4% of subjects with multi-symptom asthma had uncontrolled or poorly controlled asthma compared with 28.2% among subjects with other asthma ($p <0.001$).

Demographics and exposures

Multi-symptom asthma was significantly associated to exposure to occupational gas, dust or fumes compared to both non-asthma and other asthma (Table 3). Those with multi-symptom

asthma were more often smokers compared to other asthmatics and non-asthmatics. Those with multi-symptom asthma were on average older at disease onset, 25.0 vs. 21.6 years. There were no differences regarding the population density of the place of residence or rural or farm childhood among the groups. Only 8.0% of non-asthmatics had a family history of both asthma and allergy while this was true for 29.4% of those with multi-symptom asthma (Table 3).

Multivariate relationships

Having a family history of asthma was the strongest risk factor for multi-symptom asthma compared with non-asthma (OR 7.3, 95% CI 5.5-9.7). The ORs for having a family history of either asthma or allergy were equally strong (OR 2.6 and 2.7, respectively). Other significant risk factors included occupational exposures (OR 2.0), female gender (OR 1.6), age 61-75 (OR 1.5) and current smoking (OR 1.3) (Table 4).

When other asthma was used as a reference, family history of asthma and smoking no longer appeared as significant risk factors, and age 46-60 emerged as a new significant risk factor. For other asthma, using non-asthma as reference, female sex was not a risk factor. Old age was a protective factor for other asthma in contrast to multi-symptom asthma where old age was a risk factor.

In an additional analysis, reported allergic rhinitis was added to the model as a surrogate variable for allergic sensitisation and became the strongest single risk factor for multi-symptom asthma (OR, 4.9, data not shown). The impact of a family history of allergy was then reduced, while the impact family history of asthma did not change. The remaining variables were only marginally affected.

Attributable fraction and multiple risk factors

The AF was highest for a family history of allergy which explained 37.1% of the multi-symptom asthma in the study population (Figure 2). In addition, a family history of asthma (AF 32.8%), female gender (AF 23.7%) and occupational exposure to gas, dust or fumes (AF 16.9%) were important explanations for multi-symptom asthma. When the AF for occupational exposure to gas, dust or fumes was calculated for men and women separately, the AF for men was 35.3% and for women 12.5%, reflecting the fact that 56.0% of the men and 24.4% of the women were exposed at work.

An obvious additive risk effect on OR was seen when analysing the joint effect of family history, occupational exposure and current smoking. Using non-smoking subjects with no family history of asthma or allergy and no occupational exposure to gas dust or fumes as a reference, the OR for multi-symptom asthma for subjects with a history of both asthma and allergy, and occupational exposure and/or current smoking was 10.5 (Figure 3).

DISCUSSION

In the present population study, a subgroup of asthma with multiple symptoms has been identified. The prevalence of multi-symptom asthma was 2% in the general population and represent 24% of all asthma, a result similar to the global Asthma Insights and Reality (AIRE) survey, where the proportion of asthmatics with severe persistent asthma was 18% [1]. We hypothesise that those with multi-symptom asthma are suffering from a more severe disease, as they reported more symptoms due to environmental triggers such as cold air and dust, have significantly lower lung function, express signs of increased airway inflammation, are more hyperresponsive and have more night-time awakenings compared with those with less symptoms of asthma. Environmental load was also more important for multi-symptom asthma than for asthma in general, as occupational exposure to gas, dust or fumes, as well as smoking, were significant risk factors for multi-symptom asthma. Furthermore, obesity and female sex were more common among subjects with multi-symptom asthma. A family history of asthma and allergy were the strongest risk factors for multi-symptom asthma, particularly if both factors were present.

Frequently present in multi-symptom asthma, hyper responsiveness, airway inflammation, impaired lung function, night-time awakenings and dyspnoea, are all signs of a more severe disease, strengthening the conclusion that an epidemiological definition of multi-symptom asthma will identify subjects with more severe disease. Despite the use of asthma medication, a large majority of the multi-symptom group also have signs of uncontrolled or poorly controlled asthma as defined by GINA 2006 [17]. The definition of multi-symptom asthma used in the current study is not sufficient to encompass all aspects of severe asthma, as previously described in the literature, but many similarities are present. Firstly, “severe asthma” has primarily been investigated in clinical cohorts [2, 4, 18-20], but rarely in random population cohorts [9]. However, the current study reflects a population with signs of more severe disease, and has a gender distribution, with women being more frequently affected, that is similar to what was reported in the population based European Community Respiratory Health Survey (ECHRS) where prognostic factors for asthma severity according to GINA was investigated [9] and to the patient based ”European Network For Understanding Mechanisms Of Severe Asthma” (EMFUMOSA) [2, 21]. In the EMFUMOSA-study, allergy was inversely related to asthma severity, while in our study and in ECHRS no difference in allergic sensitisation by asthma severity was found. The EMFUMOSA study also related severe

asthma to lower FEV1% of predicted and to risk of asthma worsening upon aspirin intake [2], relationships also demonstrated in the current study.

The high proportion of asthma with multiple symptoms, despite the use of asthma medication, could be partly explained by the subjective perception of the asthma disease being controlled, despite the presence of symptoms, and therefore reduced use of prescribed medication leading to the presence of additional symptoms. This assumption is supported by population based studies showing that many patients with persistent symptoms still consider their disease "well controlled" [1, 19]. The level of asthma control falls short of the management goals with many patients being severely undertreated [1, 19, 22]. In the AIRE-study [1], the low usage of preventive medication, with many patients having to resort to quick-relief medication, is indicative of poor asthma control and a poor correlation between the level of symptoms and perceived asthma control was demonstrated. People with severe asthma are also prone to anxiety and depression, which also is associated with non-adherence to treatment regimens [21, 23, 24]. The level of asthma control is important, as it affects exacerbation frequency and quality of life [5, 17, 25, 26].

Our study shows a stronger relationship between environmental load, heredity components and multi-symptom asthma than has previously been shown for asthma in general. Thus, smoking and occupational exposure to gas, dust or fumes had a greater impact on multi-symptom asthma compared with other asthma. Occupational exposures and air pollutants are known risk factors for asthma [16] and with similar exposures at work, severe asthmatics more frequently reported that work affected their breathing [4, 27]. In particular, having a family history of both asthma and allergy seemed to have a higher importance for multi-symptom asthma than for other asthma. Heredity of allergy was a stronger risk factor for multi-symptom asthma compared to other asthma, a result that contrasts the non-random clinical cohort studied in the EMFUMOSA-project, where a negative association were reported [2, 27]. While young adulthood is a risk factor for asthma in general [10, 28], old age was a risk factor for having multi-symptom asthma. Unlike asthma in general [12, 29] no protective effect of a farm childhood could be demonstrated for multi-symptom asthma.

Chronic rhinitis was found to be more strongly related to multi-symptom asthma compared to other asthma. It has previously been shown that asthmatics with concurrent rhinitis are at a higher risk for hospitalisations and have a higher cost of asthma medication [30]. According

to population studies, 60-80% of all asthmatics have rhinitis and 20-40% of all subjects with rhinitis also suffer from asthma [28, 31, 32]. When allergic rhinitis was considered as a determinant of asthma, it appeared as the strongest risk factor for both multi-symptom and other asthma. Rhinitis has also been identified as an important risk factor of incident asthma [28, 33, 34]. In contrast to chronic rhinitis, there was no difference regarding the prevalence of allergic rhinitis among subjects with multi-symptom and other asthma.

The attributable fraction, also referred to as population attributable risk, of ever smoking, female sex, heredity and occupational exposure to gas, dust or fumes was substantial. The AF for occupational exposure has previously been estimated to 17.6% [16]. When investigating subjects with multiple risk factors, we found that the hereditary factors are the most prominent being related to increased risk of multi-symptom asthma. In the absence of a family history of asthma and allergy, an increased risk at the population level was observed only if both smoking and occupational exposure of gas dust or fumes were present. If a hereditary factor was present, the concurrent presence of smoking and/or occupational exposure to gas, dust or fumes was considerable, with a ten-fold increased risk of having multi-symptom asthma compared with subjects who have none of the risk factors. It should be noted that the cross-sectional study design do not allow for conclusions regarding causality. The identification of asthma with multiple symptoms, and the observed risk factor patterns, expands the available measures to reduce disease burden beyond pharmacotherapy. Important risk factors that could be subject to preventive measures are smoking, occupational exposures and obesity. The remaining important risk factors for other asthma in this study were female sex and heredity for asthma and allergy. From a clinical perspective, the definition of multi-symptom asthma might be an easy way to identify asthmatics in need of a more thorough follow-up and with additional management needs [17].

This large study population, that was randomly selected, allows for the identification of risk factors that are preventable. The use of questionnaire data to define severe or uncontrolled asthma is subject to limitations, why we have chosen to use the term multi-symptom asthma. When the present definition of multi-symptom asthma, based on well defined questionnaire data, was analysed, a group could be identified that differed from other asthmatics in regards to clinical characteristics and risk factor patterns. However, the questionnaire data is not sufficient to distinguish between, for instance, subjects with a persistent severe asthma and subjects with brittle asthma and lack of adherence to treatment. It might be that subjects

identified using the current method could be more sensitive to symptoms rather than having a more severe disease. The variables used in the definition of multi-symptom asthma have slightly different time spans as part of their definitions which might cause symptoms being anterior to asthma medication. This should, however, not influence the results in any great extent as a very small number of asthmatics would have had access to asthma medication before the symptoms arose. It might even be argued that some subjects with multi-symptom asthma may have some features of COPD, which however, is contradicted by the mean age of onset of asthma at 25 years and that only 9 of the smokers above the age of 50 had a FEV1/FVC ratio <0.7.

To conclude, multi-symptom asthma comprises 2% of the general population and reflects uncontrolled and more severe disease. It is associated with lower lung function, increased airway inflammation and bronchial hyperresponsiveness. Multi-symptom asthma is associated with a strong hereditary component of family history of both asthma and allergy, female sex and high BMI. Multi-symptom asthma is also linked to smoking and occupational airborne exposure to gas, dust and fumes, factors that can be prevented to reduce the burden of severe disease. We suggest that multi-symptom asthma potentially can be used as an epidemiological marker of severe disease. Identifying this group is important as they have a higher risk of being hospitalised, have more frequent contacts with health care and have a higher risk of premature death.

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TABLES

Table 1 Differences in prevalence of respiratory symptoms for subjects with multi-symptom asthma, other asthma and non-asthma.

Symptom	Multi-symptom asthma n = 367	Other asthma n = 1340	Non-asthma n = 16380
Asthma medication, %	100.0*	59.2	2.4
Attacks of shortness of breath, %	100.0*	51.3	4.1
Recurrent wheeze, %	100.0*	15.3	4.1
Any wheeze, %	100.0	56.8	12.1
Dyspnoea, %	41.1	16.4	5.0
Dust triggered, %	73.6	49.3	13.3
Strong smell triggered, %	63.8	38.1	10.9
Exercise triggered, %	78.2	48.8	15.0
Cold triggered, %	73.6	40.2	7.6
Exercise in cold triggered, %	80.4	55.8	15.5
Chronic bronchitis ever, %	22.1	10.6	2.6
Chronic productive cough, %	43.6	14.7	4.5
Chronic rhinitis, %	56.4	35.4	17.7
Allergic rhinitis, %	65.7	64.4	22.9
Difficulty breathing after use of painkiller, %	13.1	5.7	1.2
Waking with tight chest, %	59.1	26.6	6.5

P-values for comparisons between multi-symptom asthmatics vs. non-asthmatics, multi-symptom asthmatics vs. other asthmatics and other asthmatics vs. non-asthmatics were <0.001 except for allergic rhinitis (multi-symptom asthmatics vs. other asthmatics, p= 0.653). * By definition.

Table 2 Clinical characteristics for subjects with multi-symptom asthma, other asthma and non-asthma.

Variable	Category	Multi-symptom asthma n=111	Other asthma n=361	Non-asthma n=371		p-values: Multi-symptom asthma vs. non-asthma	p-values: Multi-symptom asthma vs. other asthma	p-values: Other asthma vs. non-asthma
Clinical variables								
FEV1 % of predicted, mean ±sd		88.8±21.4	98.8±18.4	104.6±16.6		**<0.001**	**<0.001**	**<0.001**
FENO, ppb at 50 ml/sec, mean±sd		29.3±29.5	23.2±17.2	19.7±13.8		**<0.001**	**0.011**	**0.004**
Methacholine reactivity, % PD20 < 1.96 mg		82.9	58.7	40.1		**<0.001**	**0.004**	**<0.001**
SPT positive	**1 positive test, %**	22.6	18.1	14.7				
	2 positive tests, %	10.8	10.7	5.1	*	**<0.001**	0.959	**<0.001**
	3 positive tests, %	8.6	10.4	1.8				
	≤ 4 positive tests, %	10.8	10.7	4.0				
	Any positive test, %	52.7	50.0	25.7		**<0.001**	0.651	**<0.001**
BMI	**BMI <20, %**	2.8	4.8	5.2				
	BMI 20-25, %	28.7	36.6	41.1	*	**<0.001**	**0.005**	**0.004**
	BMI 25-30, %	36.4	37.2	40.8				
	BMI ≥30, %	32.2	21.4	12.9				
Morbidity variables due to breathing problems last year								
Visited emergency department, %		20.7	6.1	4.0		**<0.001**	**<0.001**	0.239
Been hospitalized, %		4.5	1.4	1.1		0.034	0.057	0.749
Exacerbation ≥ 1, %		34.2	12.5	1.6		**<0.001**	**<0.001**	**<0.001**
Been on sick leave, %		7.1	4.6	1.0		**<0.001**	0.063	**<0.001**

Comparisons have been made between groups of asthma using t-tests (FEV1 % of predicted and FENO) and chi^2-tests (remaining variables), for each individual variable listed. * Mantel-Haenszel test for trend.

Table 3 Demographics for subjects with multi-symptom asthma, other asthma and non-asthma.

Exposure	Category	Multi-symptom asthma n = 367	Other asthma n=1340	Non-asthma n = 16380		p-values Multi-symptom asthma vs. non-asthma	p-values Multi-symptom asthma vs. other asthma	p-values Other asthma vs. non asthma
Occupational exposure to gas, dust or fumes, %		35.2	27.1	21.5		**<0.001**	**<0.001**	**<0.001**
Smoking	**Non-smoker, %**	51.2	55.0	58.7				
	Ex-smoker, %	23.7	26.3	22.2	*	**0.002**	**0.032**	0.152
	Smoker, %	24.3	18.1	18.5				
Area	**Gothenburg, %**	52.3	48.2	47.7				
	Town > 10 000, %	15.3	20.9	20.7				
	Town 2 000 – 10 000, %	9.5	12.8	12.0	*	0.326	0.145	0.251
	Village 500 - 2 000, %	7.9	6.0	5.9				
	Village < 500, %	15.0	12.2	13.6				
Family history	**Asthma -, Allergy -, %**	31.6	39.4	64.6		**<0.001**	**0.007**	**<0.001**
	Asthma +, Allergy -, %	6.8	8.1	5.4		0.228	0.429	**<0.001**
	Asthma -, Allergy +, %	19.6	18.3	15.4		**0.027**	0.560	**0.005**
	Asthma+, Allergy+, %	29.4	24.6	8.0		**<0.001**	0.062	**<0.001**
Rural childhood, %		37.9	38.0	38.6		0.780	0.978	0.645
Farm childhood, %		13.2	11.2	14.6		0.456	0.285	**<0.001**
Age at disease onset (years) mean±sd		25.0**±18.5**	21.6**±18.6**	-		-	**0.004**	-

Comparisons have been made between groups of asthma using chi^2-tests, for each individual variable listed, except age at disease onset where a t-test was used. * Mantel-Haenszel test for trend

Table 4 Risk factors for multi-symptom asthma and other asthma as determined by multiple logistic regression analysis.

Independent variables		Dependant variables		
		Multi-symptom asthma vs. non-asthma	**Multi-symptom asthma vs. other asthma**	**Other asthma vs. non-asthma**
Variable	**Category**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Family history	**Asthma-, Allergy-**	1	1	1
	Asthma+, Allergy-	**2.55 (1.64 - 3.97)**	1.12 (0.69 - 1.82)	**2.43 (1.95 - 3.03)**
	Asthma-, Allergy+	**2.73 (2.00 - 3.72)**	**1.55 (1.09 - 2.21)**	**1.84 (1.56 - 2.16)**
	Asthma+, Allergy+	**7.34 (5.53 - 9.74)**	**1.69 (1.24 - 2.31)**	**4.61 (3.94 - 5.38)**
Smoking	**Non-smokers**	1	1	1
	Ex-smokers	1.13 (0.86 - 1.49)	0.78 (0.57 - 1.05)	**1.43 (1.24 - 1.65)**
	Smokers	**1.31 (1.01 - 1.71)**	1.25 (0.93 - 1.69)	1.05 (0.90 - 1.22)
Age (years)	**16-30**	1	1	1
	31-45	1.02 (0.75 - 1.38)	1.01 (0.72 - 1.41)	1.01 (0.87 - 1.18)
	46-60	1.19 (0.87 - 1.62)	**1.62 (1.14 - 2.29)**	**0.74 (0.62 - 0.87)**
	61-75	**1.51 (1.09 - 2.11)**	**1.94 (1.33 - 2.82)**	**0.76 (0.63 - 0.92)**
Occupational exposure	**Yes**	**2.03 (1.61 - 2.56)**	**1.54 (1.18 - 1.99)**	**1.33 (1.16 - 1.52)**
Sex	**Women**	**1.56 (1.24 - 1.97)**	**1.38 (1.07 - 1.78)**	1.09 (0.97 - 1.23)

Risk factors, presented as Odds Ratios (OR) and 95% confidence intervals (CI). Significant differences are depicted in **bold**. All co-variates incorporated in the analysis are presented above.

FIGURE LEGENDS

Figure 1 Fraction of subjects with non-asthma, other asthma and multi-symptom asthma not reacting to an increasing cumulative dose methacholine.

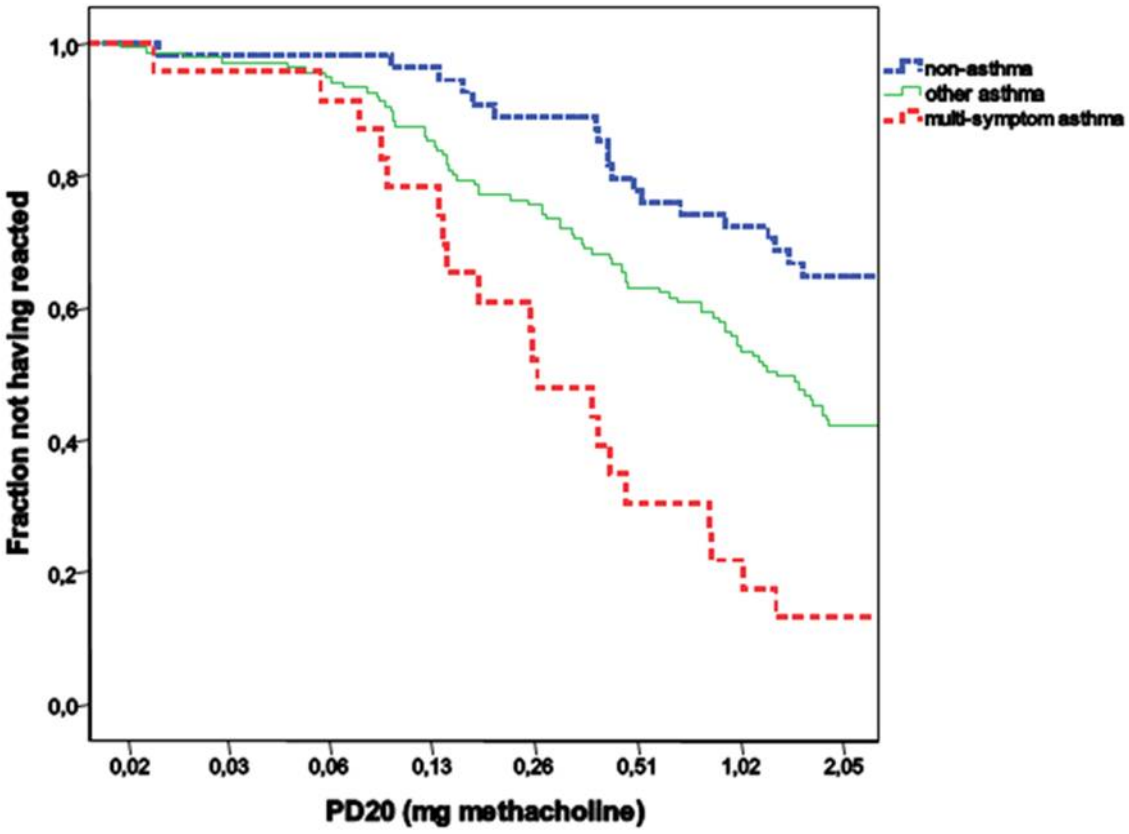

Figure 2 Attributable fractions for multi-symptom asthma.

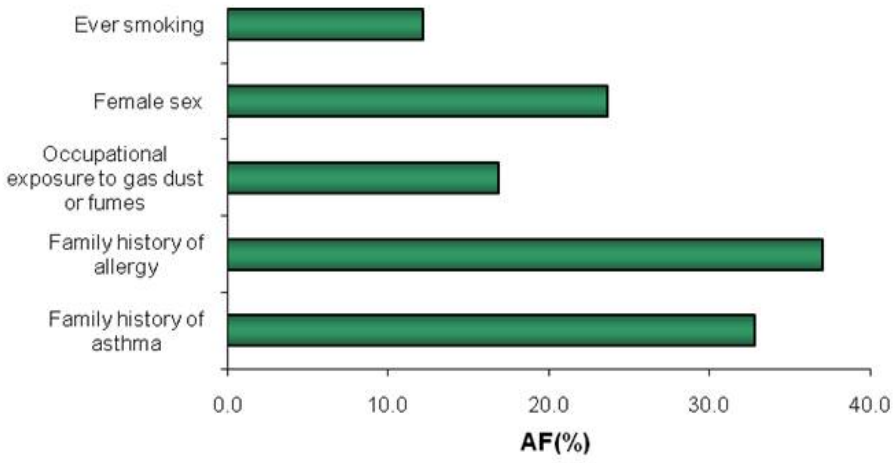

Figure 3 The effect of interaction between family history, smoking status and occupational exposure on the odds ratios for multi-symptom asthma, presented as Odds Ratios (OR) and 95% confidence intervals (CI).