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Aspirin-intolerant asthma in the population: prevalence and important determinants.

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Running head: Aspirin-intolerant asthma in the population

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Key words: Aspirin-intolerant asthma, epidemiology, risk factors, obesity, population survey

ABSTRACT

Background: Population-based studies on aspirin-intolerant asthma are very few and no previous population study has investigated risk factors for the condition.

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Objective: To investigate the prevalence and risk factors of aspirin-intolerant asthma in the general population.

Methods: A questionnaire on respiratory health was mailed to 30 000 randomly selected subjects aged 16-75 years in West Sweden, 29 218 could be traced and 18 087 (62%) responded. The questionnaire included questions on asthma, respiratory symptoms, aspirin-induced dyspnea and possible determinants.

Results: The prevalence of aspirin-intolerant asthma was 0.5%, 0.3% in men and 0.6% in women ($p=0.014$). Sick leave, emergency visits due to asthma and all investigated lower respiratory symptoms were more common in aspirin-intolerant asthma than in aspirin-tolerant asthma. Obesity was a strong risk factor for aspirin-intolerant asthma (BMI>35: OR 12.1; 95% CI 2.49-58.5) and there was a dose-response relationship between increasing body mass index and risk of aspirin-intolerant asthma. Obesity, airborne occupational exposure and visible mold at home were considerably stronger risk factors for aspirin-intolerant asthma than for aspirin-tolerant asthma. Current smoking was a risk factor for aspirin-intolerant asthma (OR 2.55; 95% CI 1.47-4.42), but not aspirin-tolerant asthma.

Conclusion: Aspirin-intolerant asthma identified in the general population was associated with a high burden of symptoms, uncontrolled disease and a high morbidity. Increasing body mass index increased the risk of aspirin-intolerant asthma in a dose-response manner. A number of risk factors, including obesity and current smoking, were considerably stronger for aspirin-intolerant asthma than for aspirin-tolerant asthma.

Abbreviations

AIA	Aspirin-intolerant asthma
ATA	Aspirin-tolerant asthma

BHR	Bronchial hyperresponsiveness
BMI	Body mass index
FeNO	Fraction of exhaled nitric oxide
FEV1	Forced expiratory volume in one second
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio

INTRODUCTION

Asthma is a common chronic disorder characterized by variable airflow obstruction, bronchial hyperresponsiveness and airway inflammation (1). Asthma is considered a syndrome rather than a single disease entity and thus comprises a number of clinical phenotypes (2, 3) as well as underlying biological endotypes (4). A subgroup of asthmatics reacts with airway obstruction upon intake of non-steroidal anti-inflammatory drugs (NSAIDs), frequently referred to as aspirin-intolerant asthma (AIA) (5). Aspirin induced dyspnea was first described in 1922 by Widal *et al.* (6), but became widely recognized first in the late 1960s as a part of the Samter's triad (7), which comprised aspirin sensitivity, asthma and nasal polyposis.

There are still limited data on the prevalence of AIA in subjects with asthma (8). Very few studies have measured the prevalence of AIA in the general population (9-11) and no previous population study has investigated risk factors for AIA.

Obesity has been identified as an independent risk factor for developing asthma (12, 13). Furthermore, obesity has been associated with a severe asthma, therapy resistance, persistent disease and low quality of life in asthmatic subjects (14, 15). Severe and therapy resistant asthma has also been associated with aspirin-intolerance (14, 16, 17). Little is known on the

relationship between AIA and body mass index (BMI), and this has not been investigated in population-based materials previously.

The aim of this study was to measure the prevalence AIA in the general adult population in West Sweden. Moreover, we sought to investigate the association between a number of risk factors, including obesity and smoking, and AIA.

METHODS

Study population and methods

In 2008, a questionnaire on respiratory health was mailed to 30 000 inhabitants in West Sweden, aged 16-75 years, of which 18 087 (62%) responded (18). A study of non-response confirmed the representativeness of the study participants (19). The study questionnaire consisted of an extended version of the OLIN questionnaire and the Swedish version of the GA²LEN questionnaire and has been previously described in detail (18).

Among responders to the questionnaire, a random selection of 2000 was invited to an extensive clinical examination. In addition, all subjects identified by the questionnaire as having asthma (Definitions, below) were invited. In total, 1052 non-asthmatics and 960 asthmatics agreed to participate, of which 41 were aspirin-intolerant. Examinations included spirometry, methacholine challenge, skin-prick tests (SPT) on a standard panel of 11 aeroallergens, anthropometric measurements, exhaled nitric oxide fraction (FeNO) determination at 50 mL*s⁻¹ flow rate, blood samples for assessment of white blood cell differential count and an extensive interview including classification of severity and control of asthma according the Global Initiative for Asthma (GINA) 2006. Detailed description of

the methods of the clinical examinations is found elsewhere (20). The study was approved by the regional ethics committee of Gothenburg.

Definitions

Classification of *asthma* was based on either (i) report of doctor's diagnosis of asthma or (ii) by self-reported ever asthma with at least one of the following conditions during the last 12 months: use of asthma medication, attacks of shortness of breath or any wheeze. *Aspirin-induced dyspnea*: "Have you ever reacted with dyspnea within three hours after taking a pain killer?" followed by a question on which specific drug that caused the reaction. Subjects specifying a drug not containing acetylsalicylic acid or a NSAID were excluded. Subjects reporting both aspirin-induced dyspnea and asthma were classed as having *aspirin-intolerant asthma* (AIA), while those reporting asthma without aspirin-induced dyspnea were classed as having *aspirin-tolerant asthma* (ATA). Body mass index (BMI): Weight in kilograms divided by the height in meters squared ($\text{kg}\cdot\text{m}^{-2}$). Definitions of the other variables used in the study are available in Table S1 in the Online Supplement.

Analyses

Statistical analyses were performed using SPSS version 17.0-20.0 (IBM Corp., Somers, NY). Comparisons of proportions were tested with Fisher's exact test. Mantel-Haenszel linear-by-linear association chi-squared test was used for testing for trends. A p-value of < 0.05 was regarded as statistically significant. Covariates used in the analyses included age, sex, BMI, family history of asthma, smoking habits, water damage at home, visible mold at home, airborne occupational exposure and farm childhood. Three logistic regression models were performed including these variables. First, the odds ratio (OR) for AIA was calculated using non-asthma as reference group; second, ATA was compared with non-asthma; and third, AIA was compared with ATA. All independent variables that had a significant OR in any of the models were included in the multiple logistic regression analyses. ORs were calculated with

95% confidence intervals (CI). Characterization of AIA and ATA was based both on questionnaire and clinical data. The observations regarding BMI, waist circumference, allergic sensitization, FEV1% predicted, BHR, FeNO, neutrophil and eosinophil blood counts, uncontrolled asthma and emergency visits were thus restricted to the smaller clinical sample. Risk factor analyses were mainly based on questionnaire data to obtain maximal statistical power.

RESULTS

Prevalence and symptoms of AIA

The prevalence of AIA was 0.5%, which was 39.3% of subjects with aspirin-induced dyspnea (Table 1). In subjects with aspirin-induced dyspnea without a diagnosis of asthma, only 32% reported occasional wheeze and 16% attacks of shortness of breath. Women had a significantly higher prevalence of AIA than men (0.6 vs. 0.3%, $p=0.014$). AIA was most common (0.7%) in ages 36-55 years, while the prevalence of ATA was highest in ages 16-35 years (10.8%) and decreased with age ($p<0.001$). Subjects with AIA comprised 5.1% of subjects with asthma. All investigated respiratory symptoms, except allergic rhinitis, were more common in AIA than in ATA (Figure 1). Whereas the prevalence of allergic rhinitis was similar in AIA and ATA, chronic rhinosinusitis was noticeably more common in AIA than in ATA (43.2 vs. 18.2%, $p<0.001$). Detailed numerical values are available in Table S2 in the Online Supplement. A considerably higher proportion of subjects with AIA reported multiple symptoms of asthma compared to subjects with ATA (Figure 2). In AIA, 40.9% reported all four investigated symptoms versus 21.0% in ATA ($p<0.001$).

Distribution of background variables

Mean BMI was higher in AIA than in ATA, both when based on self-reported data (27.6 vs. 25.9, $p=0.002$) and objective height and weight measurements (29.7 vs. 27.1, $p=0.001$) (Table

2). Several exposures were significantly more common in AIA than in ATA. This was particularly true for current smoking (34.5 vs. 16.2%, $p<0.001$) and visible mold at home (24.1 vs. 11.1%, $p<0.001$).

Clinical characteristics and morbidity

Allergic sensitization was equally common in AIA and ATA (Table 3). Moreover, there were no statistically significant differences in bronchial hyperresponsiveness, FEV1 % predicted and blood eosinophils between AIA and ATA. Neutrophils in blood was significantly higher in AIA ($4.5 \times 10^9/L$) compared to ATA ($3.8 \times 10^9/L$) and non-asthma ($3.7 \times 10^9/L$), $p=0.009$ and $p<0.001$ respectively. FeNO was lower in AIA compared to ATA (17.9 vs. 25.4 ppb, $p=0.042$) (Table 3).

Uncontrolled disease (GINA 2006) was substantially more common in AIA than in ATA (26.7 vs. 11.2%, $p=0.018$). In addition, a number of morbidity variables were more common in AIA than in ATA (Table 3). A higher proportion of subjects with AIA reported current use of asthma medication and emergency visits due to breathing problems than subjects with ATA. Further, overall sick leave, sick leave due to breathing problems and having changed occupation because of asthma was more common in AIA than in ATA.

Risk factors for aspirin-intolerant asthma

The prevalence of AIA increased markedly with increasing BMI (Figure 3). In subjects with a BMI of 35 or higher, prevalence of AIA was 2.2% as compared to 0.3-0.4% in subjects with BMI <30 . This trend remained when the analysis was limited to non-smokers, but the overall prevalence was lower. Furthermore, the association with BMI was found both in ages 16-45 years and in ages 46-75 years. When stratifying the analysis by sex, the trend was found to be strong in women, while significance was not reached in men (data not shown). Further investigation of gender specific differences in relation to AIA was not feasible due to insufficient statistical power.

Univariate logistic regression analysis was performed on a number of possible risk factors for AIA and ATA, respectively (see Table S3 in the Online Supplement). All variables that were significantly associated with either AIA or ATA in the univariate analysis were included in the multivariate analysis (Table 4). Obesity was found to be strongly independently associated with AIA compared to non-asthma in the multivariate analysis. BMI ≥ 35 yielded an OR of 12.07 (95% CI 2.49-58.5) and BMI 30-35 yielded an OR of 7.31 (95% CI 1.63-32.8). Other significant risk factors for AIA were airborne occupational exposure (OR 2.8), visible mold at home (OR 2.6), current smoking (OR 2.6), ex-smoking (OR 2.1), female sex (OR 2.3) and family history of asthma (OR 2.1). When adding chronic rhinosinusitis to the model the condition was found to be strongly associated (OR 7.6), while the other variables were only marginally affected.

When ATA was used as a reference category, statistically significant risk factors for AIA were BMI >35 (OR 6.40; 1.27-32.2), chronic rhinosinusitis (OR 2.85; 1.73-4.70), current smoking (OR 2.65; 1.49-4.71), ex-smoking (OR 1.82; 1.01-3.28), visible mold at home (OR 2.12; 1.13-3.96) and airborne occupational exposure (OR 2.09; 1.28-3.41), while allergic rhinitis, female sex and family history of asthma no longer appeared as significant risk factors.

DISCUSSION

We found a prevalence of AIA of 0.5%, which is consistent with findings from previous population-based studies (9-11), thus confirming the external validity of our study. Being the first population study to perform a comprehensive risk factor analysis of AIA, we found obesity as well as a number of environmental exposures to be associated with the disease. The risk factor pattern of AIA differed considerably from that of ATA as various risk factors were unique or considerably stronger for AIA. The most important risk factor was increasing

BMI which increased the risk of AIA in a dose-response manner independently of a number of potential confounders.

Although a number of studies of asthma patients have sought to measure the prevalence of AIA (8), population-based studies on AIA are very few (9-11). A Polish study reported a prevalence of AIA of 0.6% (9), which is highly consistent with our findings. A survey conducted in Finland (11) found a prevalence of aspirin-intolerant breathlessness regardless of asthma of 1.2%, which is identical to our result. Furthermore, as a part of a larger Australian study, mainly based on asthma patients (10), the prevalence of AIA was measured also in a small population-based sample. In the population-based sample, prevalence of AIA among asthmatics was found to be 10.9%, which corresponded to 1.1% of the total population. The substantially higher prevalence of AIA reported by this study is in accordance with a generally higher prevalence of asthma and wheeze in Australia compared with many countries in northern Europe including Sweden, Finland and Poland (1).

Several studies have investigated the association between asthma and obesity (12-15). Obesity has been associated with development of asthma (12, 13) as well as with a high severity of asthma (15, 21). Furthermore, the European ENFUMOSA study identified aspirin sensitivity, sinusitis and obesity in women as being associated with a severe phenotype of asthma (14). Only one study has investigated the association between obesity and aspirin-intolerant asthma (22). In contrast to our findings, this clinical study conducted in South Korea found no significant difference in BMI between patients with AIA and patients with ATA. However, this study defined obesity as a BMI exceeding the 95th percentile of the controls and not according to the World Health Organization (WHO) classification. Owing to lower prevalence of obesity in Korea compared to Sweden (23, 24), the Korean study probably contained very few severely obese ($\text{BMI} \geq 35$) subjects, which was the group that was found to be significantly associated with aspirin-intolerance in our study.

Our finding of a significantly higher blood neutrophil count in AIA compared to ATA and non-asthmatics, respectively, is in line with a recent British study that found increased neutrophils in the bronchial mucosa in AIA compared to ATA (25). Furthermore, a Korean study found increased levels of neutrophil activation markers in serum in aspirin-induced urticaria compared to healthy controls, arguing for a role of neutrophils in systemic inflammation as well (26). Systemic inflammation may indeed be the pathophysiological mechanism behind the correlation between obesity and AIA (27). Adipose tissue from obese individuals produce inflammatory cytokines as well as adipokines such as leptin and adiponectin (28). Leptin, which is increased in proportion to BMI and correlates with lipid status (29), has been found to induce bronchial hyperresponsiveness and elevated serum IgE levels when administered in a murine model (30). Adiponectin, which decreases with increasing visceral obesity, has been found to inhibit pro-inflammatory cytokines as well as to induce anti-inflammatory cytokines (31). In addition, there was a weak but significant cross-correlation between BMI and blood neutrophil count in our study (Figure S1).

In contrast to the association between AIA and eosinophilia found in some studies, levels of blood eosinophil counts were similar in AIA and ATA in our study. This may partly be explained by a higher use of inhaled corticosteroids in AIA than in ATA according to data from the clinical examination.

Elevated levels of leukotrienes is supposed to be a key feature in the pathogenesis of AIA (32). Thus, the findings of a correlation between BMI and granulocyte generation of leukotriene C4 (33), and an association between obesity and increased urinary leukotriene E4 in asthmatic patients (34), provide support for the hypothesis that obesity may be involved in the development of AIA.

Apart from BMI, we found that AIA differed from ATA in several aspects including gender composition, smoking habits, occupational status and exposure to various environmental

factors. In order to adjust for confounding potentially inflicted by such differences, multiple logistic regression analyses were performed for both AIA and ATA. Both AIA and ATA were confirmed as being significantly associated with obesity. However, when comparing AIA with ATA, the association with obesity was found to be considerably stronger for AIA than for ATA.

Previous studies have found a higher risk of AIA in subjects with allergy and nasal polyposis, respectively (10, 11). Bochenek et al. found that atopy was more frequent in patients with intolerance to NSAIDs than in controls (35), Valley et al. found that atopy was associated with an increased risk of AIA (10) and Hedman et al. found a 8 times higher risk of aspirin intolerant dyspnea in subjects with allergic rhinitis than in those without (11). We found that allergic rhinitis was indeed strongly associated with both AIA and ATA. However, odds ratios were similar for the two conditions, suggesting that aspirin-intolerance and allergy are separate processes in the development and maintenance of asthma (7, 16).

The importance of environmental exposures for the development of asthma is well documented (36). We found that current and former smoking, airborne occupational exposures and visible mold at home were associated with an increased risk of AIA. An American clinical study also found an association between AIA and smoking (37). Although some risk factors were shared between AIA and ATA, the risk factor patterns differed widely, suggesting a diverse pathophysiology of these two asthma phenotypes (16, 32).

Severity of asthma is difficult to measure in epidemiologic studies. However, the burden of respiratory symptoms may serve as a proxy for disease severity (20). We found a higher prevalence of a large number of respiratory symptoms in AIA than in ATA. Furthermore, having multiple symptoms common in asthma was markedly more common in AIA than in ATA. These findings suggest a higher disease severity in AIA as compared with ATA, which is in agreement with results from clinical studies (38). Moreover, we found that uncontrolled

asthma, emergency visits and sick leave due to breathing problems and changing work due to asthma were all more than twice as common in AIA than in ATA. These data suggest that AIA is associated with high morbidity, thus causing a substantial burden both on the sufferers and the society.

The current study benefits from its population-based design, large sample size and the use of well validated questions. The study is the largest population-based study on AIA to date (i.e. 18087 vs. 12971 Kasper *et al.* (9), 4300 Hedman *et al.* (11) and 1298 Valley *et al.* (10)). The response rate (62%) is comparable to other recent European studies and a study of non-response confirmed the participants as being highly representative for the population in the studied area (19). The association between AIA and BMI was preserved when BMI was based on measured height and weight in the clinically examined subsample, which confirms the validity of our results. Overall BMI was higher when based on measured height and weight than when based on self-reported data. This may be explained by the fact that subjects were weighed with indoor clothing in the clinic. Another possibility is underestimation of self-reported weight, which would however not lead to an overestimation of the association with AIA. There are no published results verifying aspirin-intolerance by provocation tests on population-based data. However, in a clinical study, history of aspirin hypersensitivity in asthmatic patients yielded a positive predictive value of 57% for AIA defined as a positive oral provocation test (39). Confirmation of aspirin intolerance by oral or inhaled aspirin provocations would have strengthened our results further. However, we did not receive approval for aspirin challenges by the regional ethics committee. Instead, the questionnaire variable on AIA was validated by telephone interviews. Among the 41 subjects with AIA that participated in the clinical examinations, telephone numbers were available for 39. Among these, 27 (69%) could be reached and agreed to participate, among whom AIA was confirmed in 19 (70%). Avoidance of aspirin and NSAID in certain subjects may have left some cases

of AIA unrecognized. However, major underdiagnosis is not probable since these drugs are widely used in the studied area. Among older smokers with asthma, some may also meet the criteria for COPD. However, it is not probable that misclassification with COPD biased our results in any major way since the association between AIA and obesity was found also when limiting the analysis to ages 16-45 years. Furthermore, since symptoms of asthma were uncommon among subjects with aspirin-induced dyspnea without asthma, the large majority in this group is not likely to have asthma. It is further unlikely that use of oral corticosteroids confounded the association between obesity and AIA since no subject with AIA used oral corticosteroids on a regular basis (data from the clinical examination).

In conclusion, as the first population based study specifically addressing risk factors for AIA, we found that obesity as well as a number of environmental exposures, including current smoking and visible mold at home, was strongly associated with the disease. The strong positive association of AIA to increasing BMI was independent of other risk factors and potential confounders. The stronger association with obesity in AIA compared to in ATA may be related to systemic inflammation with a neutrophil component.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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TABLES

Table 1. Prevalence (%) of aspirin-intolerant asthma (AIA) and aspirin-tolerant asthma (ATA) by age and sex.

			AIA	p-value*	ATA	p-value*
All ages:	total	n=18087	0.5		9.1	
	men	n=8190	0.3	0.014	8.2	<0.001
	women	n=9897	0.6		9.8	
16-35 years:	total	n=5723	0.4		10.8	
	men	n=2471	0.3	0.53	10.6	0.76
	women	n=3252	0.5		10.9	
36-55 years:	total	n=6515	0.7		8.7	
	men	n=2958	0.4	0.021	7.6	0.008
	women	n=3557	0.9		9.5	
56-75 years:	total	n=5849	0.4		7.8	
	men	n=2761	0.3	0.39	6.5	<0.001
	women	n=3088	0.5		9.0	

*: Difference by sex (Fisher's exact test, two-sided)

Table 2. Demographics for subjects with aspirin-intolerant asthma (AIA), aspirin-tolerant asthma (ATA) and non-asthma.

		AIA	ATA	Non-asthma	p-value		
					AIA vs. non-asthma	ATA vs. non-asthma	AIA vs. ATA
Subjects, total/clinical subset	n	88/41	1639/909	16360/1052			
Self-reported body mass index	kg*m ⁻²	27.6 (±5.7)	25.9 (±4.9)	25.1 (±4.3)	<0.001	<0.001	0.002
Observed body mass index*	kg*m ⁻²	29.7 (±7.3)	27.1 (±4.9)	26.0 (±4.1)	<0.001	<0.001	0.001
Waist circumference*	cm	96.9 (±16.7)	92.7 (±14.7)	90.6 (±12.9)	0.003	<0.001	0.077
Age	years	45.2 (±14.0)	43.3 (±16.2)	45.6 (±16.2)	0.82	<0.001	0.29
Female sex	%	68.2	59.2	54.2	0.010	<0.001	0.12
Family history of asthma	%	33.7	40.0	15.8	<0.001	<0.001	0.26
Age at asthma diagnosis	years	25.2 (±17.8)	22.3 (±18.3)				0.22
Smoking							
Nonsmokers	%	34.5	58.3	61.0	<0.001	0.041	<0.001
Ex-smokers	%	48.6	32.4	22.3	0.062	0.004	0.310
Current smokers	%	34.5	16.2	16.7	<0.001	0.59	<0.001
Water damage at home	%	24.1	15.4	13.0	0.006	0.003	0.035
Visible mold at home	%	24.1	11.1	7.9	<0.001	<0.001	<0.001
Airborne occupational exposure	%	43.0	28.1	21.5	<0.001	<0.001	0.005
Rural childhood	%	30.2	38.4	38.6	0.12	0.89	0.14
Farm childhood	%	15.1	11.5	14.6	0.88	<0.001	0.30

Data are presented as mean (±SD) or %. Bold indicates statistically significant differences. *: clinically examined subset.

Table 3. Characterization of aspirin-intolerant asthma (AIA), aspirin-tolerant asthma (ATA) and non-asthma based on clinical and morbidity variables.

		AIA	ATA	Non-asthma	p-value		
					AIA vs. non-asthma	ATA vs. non-asthma	AIA vs. ATA
Subjects:							
total/clinical subset	n	88/41	1639/909	16360/1052			
Clinical variables							
Allergic sensitization*	%	70.6	69.6	36.1	<0.001	<0.001	1.00
FEV1 % predicted*	%	94.3 (±18.6)	97.0 (±18.9)	105.2 (±15.0)	<0.001	<0.001	0.37
BHR*	%	71.4	60.8	33.5	0.007	<0.001	0.58
FeNO*	ppb	17.9 (±14.3)	25.4 (±21.7)	20.0 (±14.2)	0.39	<0.001	0.042
Neutrophils in blood*	10 ⁹ /L	4.45 (±2.14)	3.83 (±1.40)	3.66 (±1.33)	<0.001	0.005	0.009
Eosinophils in blood*	10 ⁹ /L	0.22 (±0.15)	0.23 (±0.17)	0.19 (±0.15)	0.18	<0.001	0.69
Morbidity variables							
Uncontrolled asthma (GINA 2006)*	%	26.7	11.2				0.018
Current use of asthma medication	%	81.8	67.6	2.3	<0.001	<0.001	0.005
Emergency visit due to breathing problems*	%	65.9	45.2	9.9	<0.001	<0.001	0.010
Hospitalized due to breathing problems	%	32.4	23.6	11.6	<0.001	<0.001	0.093
Working	%	51.7	67.0	68.8	<0.001	0.15	0.005
Sick leave	%	54.7	34.8	28.4	<0.001	<0.001	0.002
Sick leave due to breathing problems	%	12.3	5.2	1.0	<0.001	<0.001	0.016
Changed work due to asthma	%	14.5	7.1				0.032

Data are presented as mean (±SD) or % unless otherwise stated. Bold indicates statistically significant differences. *: clinically examined subset. BHR: Bronchial hyperresponsiveness.

Table 4. Risk factors (OR 95% CI) for aspirin-intolerant asthma (AIA) and aspirin-tolerant asthma (ATA) by multivariate logistic regression analysis. Independent variables were obtained from the participants in the questionnaire (n=18087).

Independent variables		Dependent variables		
		AIA vs. non-asthma OR (95% CI)	ATA vs. non-asthma OR (95% CI)	AIA vs. ATA OR (95% CI)
Female gender		2.30 (1.39-3.82)	1.23 (1.09-1.38)	1.59 (0.94-2.68)
Body mass index	≤20	1	1	1
	>20 ≤25	2.59 (0.61-10.99)	0.95 (0.76-1.18)	2.66 (0.61-11.53)
	>25 ≤30	2.67 (0.61-11.75)	1.14 (0.91-1.44)	2.46 (0.55-11.04)
	>30 ≤35	7.31 (1.63-32.8)	1.63 (1.25-2.12)	3.90 (0.84-18.1)
	>35	12.07 (2.49-58.5)	1.85 (1.31-2.62)	6.40 (1.27-32.2)
Age	16-35 years	1	1	1
	36-55 years	1.13 (0.65-1.94)	0.74 (0.65-0.85)	1.25 (0.70-2.23)
	56-75 years	0.70 (0.36-1.35)	0.69 (0.60-0.80)	0.75 (0.38-1.49)
Family history of asthma		2.14 (1.31-3.49)	3.37 (3.01-3.77)	0.65 (0.39-1.08)
Smoking	Non-smoker	1	1	1
	Ex-smoker	2.13 (1.21-3.76)	1.24 (1.08-1.42)	1.82 (1.01-3.28)
	Current smoker	2.55 (1.47-4.42)	0.95 (0.82-1.10)	2.65 (1.49-4.71)
Airborne occupational exposure		2.77 (1.72-4.48)	1.38 (1.22-1.57)	2.09 (1.28-3.41)
Visible mold at home		2.63 (1.45-4.74)	1.31 (1.08-1.57)	2.12 (1.13-3.96)
Water damage at home		1.54 (0.87-2.73)	1.08 (0.92-1.27)	1.31 (0.71-2.39)
Farm childhood		1.10 (0.59-2.08)	0.76 (0.64-0.90)	1.60 (0.82-3.13)

Odds ratios were adjusted for all independent variables presented. Bold indicates statistically significant associations.

FIGURE LEGENDS

Figure 1. Prevalence of respiratory symptoms and conditions in aspirin-tolerant asthma (blue bars) vs. aspirin-intolerant asthma (red bars). SOB: shortness of breath. P-values by two sided Fisher's exact test. *: $p < 0.05$. †: $p < 0.001$.

Figure 2. Presence of current asthma medication and common asthma symptoms in aspirin-tolerant asthma vs. aspirin-intolerant asthma. Symptoms were: attacks of shortness of breath, recurrent wheeze and at least one out of dyspnea, breathlessness at exertion, breathlessness at cold and breathlessness at exertion in cold. P-values by two sided Fisher's exact test.

Figure 3. Prevalence of aspirin-intolerant asthma by body mass index. P-value for trend was calculated by Mantel-Haenszel chi squared test.