Risk factors of severe adult-onset asthma: a multi-factor approach

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Abstract

Background The aim was to identify risk factors of severe adult-onset asthma. Methods We used data from 1350 population-based asthmatics (Adult Asthma in Finland) with adult-onset asthma (age range 31-93 years) from Finnish national registers. Severe asthma was defined as self-reported severe asthma AND asthma symptoms causing much harm AND regular impairment AND (≥1 oral corticosteroid course/year OR regular oral corticosteroids OR wake up in the night due to asthma symptoms/wheezing attach ≥ a few times/month). Sixteen covariates covering several domains (personal characteristics, education, life-style, early life factors, asthma characteristics and multimorbidities) were selected based on literature and were studied in association with severe asthma using logistic regressions. Results The study population included 100 (7.4%) individuals with severe asthma. In a univariate analysis, severe asthma was associated with male sex, age, low education, no professional training, ever smoking, ≥ 2 siblings, ≥ 1 chronic comorbidity and Non-steroidal anti-inflammatory drug (NSAID) -exacerbated respiratory disease (NERD) ($p<0.05$); and trends for association ($p<0.2$) were observed for severe childhood infection, presence of chronic rhinosinusitis with nasal polyps, and being the 1 st child. The 10 variables (being 1 st child was removed due to multicolinearity) were thus entered in a multivariate regression model and severe asthma was significantly associated with male sex (OR [CI95%] = 1.96 [1.16-3.30]), ever smoking (1.98 [1.11-3.52]), chronic comorbidities (2.68 [1.35-5.31]), NERD (3.29 [1.75-6.19]), and ≥ 2 siblings (2.51 [1.17-5.41]). There was a dose-response effect of the total sum of these five factors on severe asthma (OR [CI95%] = 2.30 [1.81-2.93] for each increase of one unit of the score). Conclusions Male sex, smoking, NERD, comorbidity, age and number of siblings were independent risk factors for self-reported severe asthma. The effects of these factors seem to be additive; each additional risk factor gradually increase with the risk of severe asthma.

Background

The prevalence of asthma has strongly increased over the past decades, and about 10% of the population in industrialized countries ever had asthma (1). Asthma is a heterogeneous disease, and among the various asthma characteristics involved in the disease phenotypic heterogeneity, both clinical observations and statistical cluster based approaches identified age at asthma onset as a key differentiating factor (2–5). Asthma often starts early in life, but asthma can appear in adulthood and adult -onset asthma has been the focus of less attention. In relation to childhood-onset asthma, adult-onset asthma is associated with more respiratory symptoms, asthma medication use (6) and with a poorer prognosis (7). Adult-onset asthma demonstrates multiple phenotypes and severe adult-onset asthma is of particular concern and requires further investigations.

Severe asthma represents approximatively 5–10% of patients with asthma (8), and a recent Finnish cohort of unselected patients with adult-onset asthma estimated that 5.9% fulfilled ERS/ATS severe asthma definition (9). Defining severe asthma is uneasy, particularly in epidemiological research, since several definitions of severe asthma have been proposed to guide asthma management (GINA, ERS/ATS, WHO), with poor agreement between some of them, and often not directly applicable in epidemiological

studies (10). Nevertheless, several risk factor have been proposed for severe asthma in adults, including type2 inflammation (eosinophilia) (11–13), older age (14), low socioeconomic status (15, 16), atopy (16), Non-steroidal anti-inflammatory drug (NSAID) -exacerbated respiratory disease (NERD) or NSAID-triggered exacerbation (17), rhinosinusitis associated with nasal polyps (18), sensitization to *Staphylococcus aureus* enterotoxins (19) or to *fungi* (20), smoking or asthma-chronic obstructive pulmonary disease (COPD) overlap (21, 22). Contradictory results have been observed regarding gender (21, 23). However severe adult asthma combines both persistent childhood-onset asthma and adult-onset asthma, two distinct phenotypes, with possibly different risk factors. To our knowledge, few studies have specifically focused on severe adult-onset asthma (14), and except smoking (22), risk factors for severe adult-onset asthma remain poorly characterized.

Early detection of the risk factors contributing to severe adult-onset asthma is important to decrease morbidity and costs. Most previous results have focused on one or few risk factors, although we are facing a multifactorial phenotype. Hence, as there is still limited knowledge of the putative combination of risk factors in the development of severe adult-onset asthma, this study was carried out to identify risk factors associated with severe asthma in a large population-based case control study on adult-onset asthma (7, 24). We hypothesized that factors related to smoking, age, gender, multimorbidity, are positively associated with severe adult-onset asthma and that the severe asthma risk increases with the number of these risk factors.

Methods

Study design

This is a cross-sectional population-based case-control study of adult-onset asthma in Finland. We used a questionnaire of childhood and adulthood factors in 1996-97.

Setting

Population-based sample of asthmatics of Finland and their matched controls.

Study Population

The Adult Asthma in Finland is a population-based matched case-control study conducted in 1997 (Figure 1) as previously described (24). This study collected information from 1350 asthma patients older than 30 years of age with an asthma diagnosis. Of this asthma population, 182 asthmatics were from the longitudinal, population-based Mini Finland Health Survey, and 1168 were recently diagnosed asthmatics randomly drawn from the Finnish Drug Reimbursement register maintained by Social Insurance Institution (SII) of Finland (25). The reimbursement right is granted by certificate that has been made by patient´s physician and includes background information, clinical exam´s results, lung function test results as well as findings and conclusions after asthma treatment test period of 6 months. All asthmatics fulfilled the following criteria for doctor-diagnosed asthma in this register: typical history, clinical features, and asthma course, at least one of the following physiologic criteria: (i) a variation of

20% or greater in diurnal peak expiratory flow (PEF) recording (reference to maximal value); (ii) an increase of 15% or greater in PEF or forced expiratory volume in 1 second (FEV1) with b-agonist; or (iii) an decrease of 15% or greater in PEF or FEV1 in exercise testing. This method of case ascertainment has been validated earlier(26,27). In addition, the asthmatics had self-reported onset of asthma symptoms and/or asthma diagnosis after 15 years of age. Questionnaire consisted of demographic questions and asthma-specific questions. The proportion of the responders in asthma group was 86.1%. Approval for the study was obtained from the ethical committee at Tampere University Hospital and a written consent was obtained from all subjects.

Outcomes

The individuals with asthma were asked the year of doctor-diagnosed asthma and the age of onset of asthma symptoms, a) in childhood, b) at school age, c) over 15 years of age, d) in adulthood. Among asthmatics who fulfilled the selection criteria (detailed above), those responded that the onset of asthma symptoms and/or the age of asthma diagnosis was 16 years or over were defined as adult-onset asthma. Mean age (SD, min-max) of doctor-diagnosed asthma was 49.8 (11.8, 16-90) years, and 90.8% reported that their asthma symptoms had been started in adulthood (d). Severe asthma (Sev-Q) was defined as self-reported severe asthma AND asthma symptoms causing much harm AND regular impairment AND (≥1 oral corticosteroid course/year OR regular oral corticosteroids OR wake up in the night due to asthma symptoms/wheezing attach ≥ a few times/month).

Covariates

Fifteen covariates were a priori selected based for their potential impact on severe asthma from the data reported in literature:

- Personal characteristics (3 factors): gender (21,23,28), age (< vs. ≥ 50 years) (14), body mass index (BMI) (<30 vs. ≥ 30 kg/m^2) (29)(30)
- Socio-economic characteristics (2 factors): education level (baccalaureate/secondary vs. primary school) professional training (completed professional college/university/courses/completed trade school vs. no) (15,16,31)
- Lifestyle factors (1 factor) : smoking (never vs. ever) (21,22,32)
- Early-life factors (6 factors): growing in countryside/farm (33), parental smoking (34), parental asthma and/or allergy (35), severe childhood infections (pneumonia before or during school age or hospitalization due to infection at ≤3 years of age) (36), number of siblings (<2 vs. ≥ 2) (24), birth order (1st vs. other) (24,37,38)
- Asthma characteristics (1 factor): non-steroidal anti-inflammatory drug (NSAID) – exacerbated respiratory disease (NERD) (17)
- Chronic comorbidities (3 factors): ≥1 other allergic disease ever [e.g. allergic rhinitis (AR)/allergic conjunctivitis (AC)/atopic dermatitis (AD)] (16,24), nasal polyps (NP) (18), ≥1 other chronic disease(s) (7,21,32).

Statistical analysis

The associations between each risk factor and severe asthma were estimated using chi-square (dichotomous) and t-test (continuous), and by using univariate logistic regressions. Odds ratios (OR) with 95% confidence intervals are reported. Risk factors associated with severe asthma with a p value below 0.2 were included in a multiple logistic regression model. Risk factors that were statistically significantly associated with severe asthma ($p<0.05$) in the multiple logistic were combined in a risk score defined as the sum of the risk factors. The association between the risk score and severe asthma was assessed by logistic regression model. A sensitivity analysis was conducted to address the robustness of the association to the definition of severe asthma, and in particular using a medication-based definition of severe asthma (Sev-OCS) with severe asthma defined by the report of oral corticosteroid in regular use or ≥ 2 courses/year due to asthma. Statistics were performed with SPSS Base 24 Statistical Software Package (SPSS, Chicago, IL, USA).

Results

Population description

The study flow chart is shown in the Fig. 1. The total number of adult-onset asthma cases with available data was 1350. Mean age (SD, min-max) was 54.4 (12.2, 31–93) years. The proportion of females was 62.1%, and the proportion of subjects reporting at least secondary school level of education was 36.1%. A hundred subjects (7.4%) reported severe asthma. Severe asthma was associated with increased number of work impairment days due to respiratory symptoms (1.006 [1.003–1.009] for each increase of one work impairment day, $p < 0.001$). Nineteen (19.0%) severe asthmatics and 109 (8.7%) non-severe asthmatics reported work impairment over 20 days/year due to respiratory symptoms ($p = 0.002$).

Risk factors of severe adult-onset asthma

The description of self-reported demographic factors in the severe and non-severe asthma groups is shown in Table 1. In unadjusted analysis, severe adult-onset asthma was statistically significantly associated with male sex, higher age, low education, no professional training, ever smoking, ≥ 2 siblings, ≥ 1 chronic comorbidity and Non-steroidal anti-inflammatory drug (NSAID) -exacerbated respiratory disease (NERD) ($p<0.05$, Table 2, Model 1). In addition, there was a trend for an association ($p<0.2$) with severe childhood infection, NP, and being the 1st child (Table 2, Model 1). The variable being the 1st child was strongly associated with ≥ 2 siblings and therefore was not considered in the multivariate analysis due to multicollinearity (Table 2). Thus the 10 variables were entered in a multivariate regression model and severe adult-onset asthma (Sev-Q) was significantly associated with male sex (OR [CI95%] = 1.96 [1.16-3.30]), ever smoking (1.98 [1.11-3.52]), chronic comorbidities (2.68 [1.35-5.31]), NERD (3.29 [1.75-6.19]), and ≥ 2 siblings (2.51 [1.17-5.41]) ($p<0.05$, Table 2, Model 2 and Figure 2).

When counting the total sum of the five risk-factors, 27 (2.0%), 188 (13.9%), 433 (32.1%), 398 (29.5%) 260 (19.3%) and 9 (0.7%) had, 0, 1, 2, 3, 4 5 risk factors, respectively. Risk for severe adult-onset asthma significantly and gradually increased with the sum of the five risk factors (OR (CI95%) = 2.30 [1.81-2.93] for each additional unit, p<0.001). A significant dose response effect was also detected by using this sum variable (Table 3).

Sensitivity analysis

The total number of severe asthmatics by using oral corticosteroid-based definition was 226 (16.7%). Forty-one (41.0 %) of the questionnaire-based (Sev-Q) severe asthmatics had also oral corticosteroid-based (Sev- OCS) severe asthma (p<0.001). Thirty-seven (16.4%) severe asthmatics (Sev-OCS) and 91 (8.1 %) non-severe asthmatics reported work impairment over 20 days/year due to respiratory symptoms (p=0.001).

In univariate models, Sev-OCS was associated with the following four variables at p<0.05 level: ever smoking, being the first child, growing in countryside/farm, ≥ 1 chronic comorbidity; and with a trend (e.g. at p<0.2 level): high BMI, parental smoking, severe childhood infection, NERD (Table 4, Model 1). Age (p=0.20) and sex (p=0.21) were entered in the multivariate model for comparability with the main analysis. When entering these 10 variables in a multivariate logistic regression model, severe adult-onset asthma (Sev-OCS) was significantly associated with ever smoking, growing in countryside/farm, NERD, and ≥ 1 other chronic disease (p<0.047, Table 4, Model 2).

Discussion

In this population-based case-control study of adult-onset asthma, severe asthma was associated with male sex, smoking, NERD, comorbidity, and the number of siblings. Noteworthy, associations for smoking, NERD and comorbidity were found in a sensitivity analysis based on another asthma severity definition, indicating that these associations were robust to the asthma severity definition. The effects of these risk factors seem to be additive; each additional risk factor gradually increases the risk of severe asthma.

In our study population the prevalence of severe asthma was 7.4% of patients with adult-onset asthma. This is in line with previous observations, in which the prevalence of severe asthma has been estimated to vary between 5–10% of patients with asthma (8). A Finnish single-center (central hospital) cohort of unselected patients with adult-onset asthma estimated that 5.9% fulfilled ERS/ATS severe asthma definition (9). This lower proportion could be explained by slightly different definition of severe asthma than in our study.

Our results reinforced previous findings regarding the impact of NERD, smoking and comorbidities in severe adult-onset asthma. A systematic review identified 27 publications, in which the prevalence of NERD among asthmatics was about 7%, and it was the highest among severe asthmatics (17). Korea Severe Asthma Registry analysis (n = 489) showed that individuals with severe asthma (including early- and adult-onset) have comorbidities such as allergic rhinitis (59%), atopy (39%), Aspirin hypersensitivity

(14%) (39). Severe asthma and/or NERD has been shown to be associated with Type2 inflammation (11). Our findings could support that NERD, often characterize by a Type2 inflammation in literature (40), is one of the important risk factors of severe adult-onset asthma. Consistently with the literature, smoking and comorbidities were important independent factors of severe adult-onset asthma in our study. The deleterious effect of smoking in subjects with asthma has well been demonstrated in the literature, with decreased lung function (37), increased asthma severity (41), and risk of mortality (8). A cohort of Finnish middle-age asthmatics (including early- and late-onset) (n = 529) showed that 8% of the asthmatics, with more severe asthma and comorbidities, had poorer Work Ability Score during 10-year-follow-up (1).

Our study identified that independently of age and other factors, the presence of ≥ 2 siblings was a risk factor of severe adult-onset asthma. Professional training was associated with a lower risk of severe asthma, although the association was borderline significant in the multiple logistic regression. In our study population (who was born between 1904 and 1966), it could be speculated that the presence of ≥ 2 siblings could reflect poorer early living conditions predisposing to lower SES also in adulthood (42), which thus may have an impact on asthma self-care behavior (43). A study of elderly French women (n = 2258) showed that a low educational level (11%) was associated with an increased risk of uncontrolled asthma (including early- and late-onset cases) (15). In agreement with the hygiene hypothesis, number of siblings has been suspected to protect against the development of childhood asthma (44) and other atopic diseases (45). On the other hand, number of siblings might be a risk factor for asthma and lower lung function because it might lead to increase contact with pathogens that cause lower respiratory infections (46) and may lead to exacerbated asthma especially in genetically predisposed individuals (47).

Regarding gender, the main analysis showed a higher risk of severe adult-onset asthma in men as compared to women, but the sensitivity analysis using the OCS-based definition did not. This could reflect that male asthmatics reporting more difficult symptoms, could have OCS-resistant asthma such as smoking-related inflammation (48).

Our study did not detect an association between self-reported history of severe childhood infection(s) and severe adult-onset asthma, which might be due to the fact that childhood infections increase risk of exacerbated childhood onset asthma (47), more than severe adult-onset asthma. Another possible explanation might be related to measurement error/cohort effect as during the decades when our study population was born, the treatment of childhood infections has changed due to increased availability of public children´s counseling, doctors and antibiotics. There is no or little previous evidence of childhood infections on severe adult-onset asthma. In Tasmanian Longitudinal Health Study (n = 7312) a history of pneumonia before age of 7 year was ascertained from parents and measles, rubella, mumps, chickenpox, diphtheria, and pertussis from school medical records (36). Greater infectious diseases load was negatively associated with persisting asthma at all ages (36).

Presence of allergic disease(s) (AR and/or AC and/or AD) was not associated with the risk of severe adult-onset asthma in our study. In terms of mortality among asthmatics and matched controls, our

previous study has shown that presence of AR or AC did not explain excess mortality among asthmatic adults (7), which is in line with our current findings. Overall, it is likely that asthma with allergic multimorbidity represent phenotypes that considerably differ from asthma alone in terms of mechanisms, severity and prognosis. Further studies in younger populations are needed as we demonstrated earlier that the association between allergic multimorbidity and asthma differs with age, with a stronger association observed in the youngest (24).

Although there is growing evidence that early-life factors play a role in the development of asthma (i.e. parental smoking, infection, nutrition, rural environment) (49), whether these early-life factors are associated with severe adult-onset asthma remain to be addressed. In our study, growing in the countryside, or parental asthma/allergy/smoking were not associated with severe adult-onset asthma in the main analysis, but the sensitivity analysis resting on the OCS-based definition of severe asthma showed a significant association with growing in countryside/farm. This could reflect OCS-sensitive inflammation (such as allergic fungal asthma). Other studies have shown that farm environments represent a source of fungi and increase asthma risk, and that sensitization to fungi might be related to severe asthma (20), and the severity of allergic fungal asthma can be decreased by OCS (50). Our previous analysis discovered association between sensitization to Aspergillus fumigatus and asthma in adult population (51).

Previous studies have shown that obesity increase the odds of a more persistent and severe asthma phenotype (52), and that obesity-associated severe asthma may represent a distinct clinical phenotype (53). Yet, we did not detect an association between BMI and severe adult-onset asthma in the main analysis, but a trend for a positive association was observed when using the medication-based definition of severe asthma.

This study presents several strengths, among which the outcome definition. In this population-based study, a specific definition of asthma was used, based on lung-function test confirmed doctor-diagnosed asthma. In addition, asthma is a spectrum of inflammatory lower airway conditions with variable obstruction, and heterogeneous background. Many epidemiological studies aiming at identifying risk factors for asthma did not consider this heterogeneity in the disease expression, which may affect interpretation and comparison of results between studies. In this study, we look for risk factors of severe adult-onset asthma, a specific phenotype associated with poor prognosis, with a definition of severity combining several domains of the disease. A further strength relies in the analytical approach consisting in estimating the joint effect of multiple risk factors and in addressing the robustness of the results to the definition of severe asthma. We chose two severe asthma definitions, based on data available in order to test the robustness of our findings to the definition of severe asthma. Although only 41% of cases had severe asthma by both Sev-Q and Sev-OCS definitions, these two severe asthma definitions showed consistency for three risk factors (smoking, comorbidities and NERD), supporting the role of these factors in severe asthma.

The weaknesses of our study include the limited statistical power of multivariable analyses. Due to cross-sectional design we were not able to evaluate the causal direction of associations, however because asthma was recently diagnosed (past year) given to the study design, covariates should have occurred before development of adult-onset asthma. We acknowledge that we lacked the lung function test data as an additional objective measurement of severe asthma and that a small portion of asthmatics might had childhood-onset asthma that relapsed in adulthood. In addition, a memory bias in the report of risk factors might have occurred. Finally, the associations reported could be partly biased by residual for confounding, either due to missing potential confounders in the regression model (such as occupational exposure), or due to limited accuracy in the assessment of some independent variables (i.e. the smoking variable does not consider the amount and the duration of smoking). Thus, before extrapolating our results, replication studies are needed.

Conclusion

Our study indicates that male sex, smoking, NERD, comorbidity, ≥ 2 siblings are independent risk factors for self-reported severe adult-onset asthma. Although these results need validation in other populations, in terms of clinical implication they reinforce the need for smoking cessation and the importance of diagnostics and management of NERD and other comorbidities to prevent severe asthma in adult-onset asthma patients.

Abbreviations

AC = allergic conjunctivitis

AD = allergic dermatitis

AR = allergic rhinitis

CI = confidence interval

FEV1 = forced expiratory volume during the first second

ICS = inhaled corticosteroid(s)

NERD = non-steroidal anti-inflammatory drug (NSAID) exacerbated respiratory disease

OCS = oral corticosteroid(s)

OR = odds ratio

PEF = peak expiratory flow

SABA = short-acting beta agonist(s)

SII = Social Insurance Institution of Finland

Declarations

Ethics approval and consent to participate

Approval for the study was obtained from the ethics committee at Tampere University Hospital (2/1996) and a written consent was obtained from all subjects.

Competing interests

STS reports a grant of GSK and consultancies for ERT, Novartis, Sanofi Pharma and Roche. SC reports personal fees from AstraZeneca, non-financial support from Boehringer Ingelheim, non-financial support from Actelion Pharmaceuticals, non-financial support from MSD, non-financial support from Astellas. JK reports personal fees from ALK, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, MSD, Mundipharma, Novartis, Orion Pharma, Teva. JB reports personal fees and other from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Sanofi-Aventis, Takeda, Teva, Uriach, other from Kyomed INNOV. All these are outside the submitted work. All other authors declare no conflicts of interest.

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Authors' contributions

All authors participated on the planning and conception of the study and the analytical strategy, STS, RL and VS performed the data analyses and wrote the manuscript. All authors have assisted in data management, analyses and critical review of the manuscript.

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Tables

Table 1. Association between self-reported demographic factors and severe and non-severe asthma groups.

	Non-severe asthma n=1250	Severe asthma n=100	p
Personal characteristics			
Female gender, n (%)	793 (63.4)	45 (45.0)	**<.001**
Age, years, mean(SD)	54.0 (12.2)	58.7 (11.6)	**.001**
BMI[1], mean (SD)	26.9 (4.7)	27.1 (5.5)	.94
Socio-economic characteristics			
Baccalaureate/secondary school, n (%)	754 (61.8)	71 (76.3)	**.005**
Professional training, n (%)	296 (26.0)	35 (40.7)	**.004**
Lifestyle factors			
Ever smokers, n (%)	720 (57.6)	74 (74.0)	**.001**
Early-life factors			
1st child, n (%)	363 (29.0)	22 (22.0)	.14
≥ 2 siblings, n (%)	927 (75.9)	84 (89.4)	**.003**
Growing in countryside/farm, n (%)	937 (75.9)	77 (80.2)	.39
Severe childhood infections[2], n (%)	217 (18.0)	11 (11.7)	.13
Parental smoking, n (%)	648 (51.8)	53 (53.0)	.84
Parental asthma and/or allergy, n (%)	437 (36.1)	29 (29.9)	.23
Asthma characteristics			
NERD, n (%)	124 (9.9)	19 (19.0)	**.007**
Multimorbidity			
CRSwNP, n (%)	145 (11.6)	7 (7.0)	.19
≥ 1 other disease[3], n (%)	843 (67.4)	86 (86.0)	**<.001**
≥ 1 other allergic disease (AR/AC/AD), n (%)	844 (67.5)	63 (63.0)	.38

NERD = patient-reported NSAID-exacerbated respiratory disease; CRSwNP= chronic rhinosinusitis with nasal polyps; AR= allergic rhinitis; Ac = allergic rhinoconjunctivitis, AD= atopic dermatitis. P values by Chi square test (dichotomous) or t-test (continuous variables). P value less than 0.05 were considered significant. [1]The BMI-data was missing from 6 (6.0 %) severe asthmatics and 29 (2.3 %) non-severe asthmatics. [2]pneumonia before or during school age and/or hospitalization due to infection at ≤3 years of age. [3]Hypertension (n=298), coronary artery disease (n=120), Rheumatoid arthritis (n=60), psychiatric disease/disorder (n=86), diabetes (n=54), glaucoma (n=49), musculoskeletal disease/back pain (n=367), arthritis (n=244), empyema (n=106), other chronic disease(s) except chronic bronchitis/bronchiectasis (n=449). Education level = baccalaureate/secondary vs. primary school; professional training = completed professional college/university/ courses/trade school vs. no professional training. Severe asthma (Sev-Q) was defined as self-reported severe asthma AND asthma symptoms causing much harm AND regular impairment AND (≥1 oral corticosteroid course/year or regular oral corticosteroids AND/OR wake up in the night due to asthma

symptoms/wheezing attach ≥ a few times/month). Missing values were included and regarded as ”no”.

Table 2. Association of risk factors with severe adult onset asthma by using question-based definition of severe asthma (Sev-Q).

		Model 1 Univariate regression model		Model 2 Multiple regression model n=1173	
		OR_1 (95% CI)	p_1	OR_2 (95% CI)	p_2
Male gender	no	1	**<.001**	1	**.011**
	yes	2.12 (1.41-3.20)		1.96 (1.16-3.30)	
Age[1]		1.033 (1.02-1.05)	**<.001**	1.002 (0.98-1.03)	.88
BMI[1]		1.010 (0.97-1.06)	.66	Not entered	
Baccalaureate/secondary school	no	1	**.006**	1	.70
	yes	0.50 (0.31-0.82)		0.88 (0.48-1.65)	
Professional training	no	1	**.003**	1	.074
	yes	0.51 (0.33-0.80)		0.62 (0.36-1.05)	
Ever smokers	no	1	**.002**	1	**.020**
	yes	2.10 (1.32-3.32)		1.98 (1.11-3.52)	
1st child	no	1	**.14**	Not entered[2]	
	yes	0.69 (0.42-1.12)			
≥ 2 siblings	no	1	**.004**	1	**.018**
	yes	2.66 (1.37-5.20)		2.51 (1.17-5.41)	
Growing in countryside/farm	no	1	.34	Not entered	
	yes	1.29 (0.77-2.17)			
Severe childhood infections[3]	no	1	**.13**	1	.11
	yes	0.60 (0.32-1.15)		0.55 (0.26-1.14)	
Parental smoking	no	1	.82	Not entered	
	yes	1.05 (0.70-1.58)			
Parental asthma and/or allergy	no	1	.22	Not entered	
	yes	0.76 (0.48-1.19)			
NERD	no	1	**.005**	1	**<.001**
	yes	2.13 (1.25-3.63)		3.29 (1.75-6.19)	
CRSwNP	no	1	**.17**	1	.17
	yes	0.57 (0.26-1.26)		0.54 (0.22-1.30)	
≥ 1 other disease[3]	no	1	**<.001**	1	**.005**
	yes	2.97 (1.67-5.28)		2.68 (1.35-5.31)	
≥ 1 other allergic disease (AR/AC/AD)	no	1	.36	Not entered	
	yes	0.82 (0.54-1.25)			

Model 1 = Univariate analysis. Model 2 = Multivariable analysis by the eleven variable that were associated at p<0.2 level in the Model 1. NERD = patient-reported NSAID-exacerbated respiratory disease; CRSwNP= chronic rhinosinusitis with nasal polyps; AR= allergic rhinitis; AC = allergic rhinoconjunctivitis, AD= atopic dermatitis. [1]continuous variables. [2]The variables "1st child" and "≥2 siblings" correlated (p<0.01, r=-0.42, by Pearson´s correlation test), hence to avoid multicolinearity, only the statistically significant variable "≥2 siblings" was added into the multivariable model. [3]pneumonia before or during school age and/or hospitalization due to infection at ≤3 years of age. Education level = baccalaureate/secondary vs. primary school; professional training = completed professional college/university/ courses/trade school vs. no professional training. OR = odds ratio. CI= confidence interval. Severe asthma (Sev-Q) was defined as self-reported severe asthma AND asthma symptoms causing much harm AND regular impairment AND (≥1 oral corticosteroid course/year or regular oral corticosteroids AND/OR wake up in the night due to asthma symptoms/wheezing attach ≥ a few times/month).

Table 3. Association of the sum of the risk factors (categorized as 0-1, 2-3, and 4-5 risk factors) with severe adult onset asthma by using question based definition of severe asthma (Sev-Q).

	N total (n with severe asthma)	OR_1 (95% CI)	p_1
0-1	215 (3)	1	
2-3	831 (47)	4.24 (1.31-13.75)	**.016**
4-5	269 (44)	13.82 (4.23-45.18)	**<.001**

Risk factors were male gender, ≥2 siblings, ever smoking, NERD, ≥1 other disease. When counting the total sum of the five risk-factors, 27 (2.0%), 188 (13.9%), 433 (32.1%), 398 (29.5%) 260 (19.3%) and 9 (0.7%) had, 0, 1, 2, 3, 4 5 risk factors, respectively. Risk for severe asthma (Sev-Q) significantly and gradually increased with the sum of the five risk-factors (OR (CI95%) = 2.30 [1.81-2.93] for each additional unit, p<0.001). NERD = patient-reported NSAID-exacerbated respiratory disease. polyps; AR= allergic rhinitis; AC = allergic rhinoconjunctivitis, AD= atopic dermatitis. [1]continuous variables. OR = odds ratio. CI= confidence interval. Severe asthma (Sev-Q) was defined as self-reported severe asthma AND asthma symptoms causing much harm AND regular impairment AND (≥1 oral corticosteroid course/year or regular oral corticosteroids AND/OR wake up in the night due to asthma symptoms/wheezing attach ≥ a few times/month).

Table 4. Association of risk factors with severe adult onset asthma by using medication-based definition of severe asthma (Sev-OCS). Multivariate model.

		Model 1 Univariate regression model		Model 2 Multiple regression model n=1173	
		OR_1 (95% CI)	p_1	OR_2 (95% CI)	p_2
Male gender	no	1	**.21**	1	.87
	yes	1.20 (0.90-1.61)		1.03 (0.73-1.46)	
Age[1]		1.008 (1.00-1.02)	**.20**	1.012 (1.00-1.03)	.092
BMI[1]		1.03 (1.00-1.06)	**.059**	1.31 (0.92-1.87)	.13
Baccalaureate/secondary school	no	1	.33	Not entered	
	yes	0.86 (0.63-1.17)			
Professional training	no	1	.20	Not entered	
	yes	0.81 (0.58-1.12)			
Ever smokers	no	1	**.001**	1	**.003**
	yes	1.70 (1.25-2.31)		1.69 (1.19-2.40)	
1st child	no	1	**.043**	1	.088
	yes	1.37 (1.01-1.86)		1.34 (0.96-1.86)	
≥ 2 siblings	no	1	.62	Not entered	
	yes	0.92 (0.65-1.29)			
Growing in countryside/farm	no	1	**.041**	1	**.046**
	yes	0.72 (0.52-0.99)		0.69 (0.48-0.99)	
Severe childhood infections[2]	no	1	**.19**	1	.88
	yes	1.28 (0.89-1.84)		1.03 (0.69-1.54)	
Parental smoking	no	1	**.16**	1	.19
	yes	1.23 (0.92-1.64)		1.24 (0.90-1.69)	
Parental asthma and/or allergy	no	1	.92	Not entered	
	yes	1.02 (0.75-1.37)			
NERD	no	1	**.15**	1	**.029**
	yes	1.37 (0.89-2.11)		1.68 (1.06-2.69)	
CRSwNP	no	1	.92	Not entered	
	yes	0.98 (0.62-1.54)			
≥ 1 other disease[3]	no	1	**.001**	1	**.037**
	yes	1.73 (1.24-2.43)		1.49 (1.03-2.18)	
≥ 1 other allergic disease (AR/AC/AD)	no	1	.42	Not entered	
	yes	1.14 (0.83-1.55)			

Model 1 = Univariate analysis. Model 2 = Multivariable analysis by the twelve variable that were associated at p<0.2 level in the Model 1.). In addition, we wanted to force age (p=0.20) and sex (p=0.021) in the model 2 to get more comparable model to the first one. Hence a total of 10 variables were entered in a multivariable model. NERD = patient-reported NSAID-

exacerbated respiratory disease; CRSwNP= chronic rhinosinusitis with nasal polyps; AR= allergic rhinitis; AC = allergic rhinoconjunctivitis, AD= atopic dermatitis. [1]continuous variables. [2]pneumonia before or during school age and/or hospitalization due to infection at ≤3 years of age. Education level = baccalaureate/secondary vs. primary school; professional training = completed professional college/university/ courses/trade school vs. no professional training. OR = odds ratio. CI= confidence interval. Severe asthma (Sev-OCS) was defined as those who reported peroral corticosteroid in regular use and/or ≥ 2 course/year due to asthma.

Figures

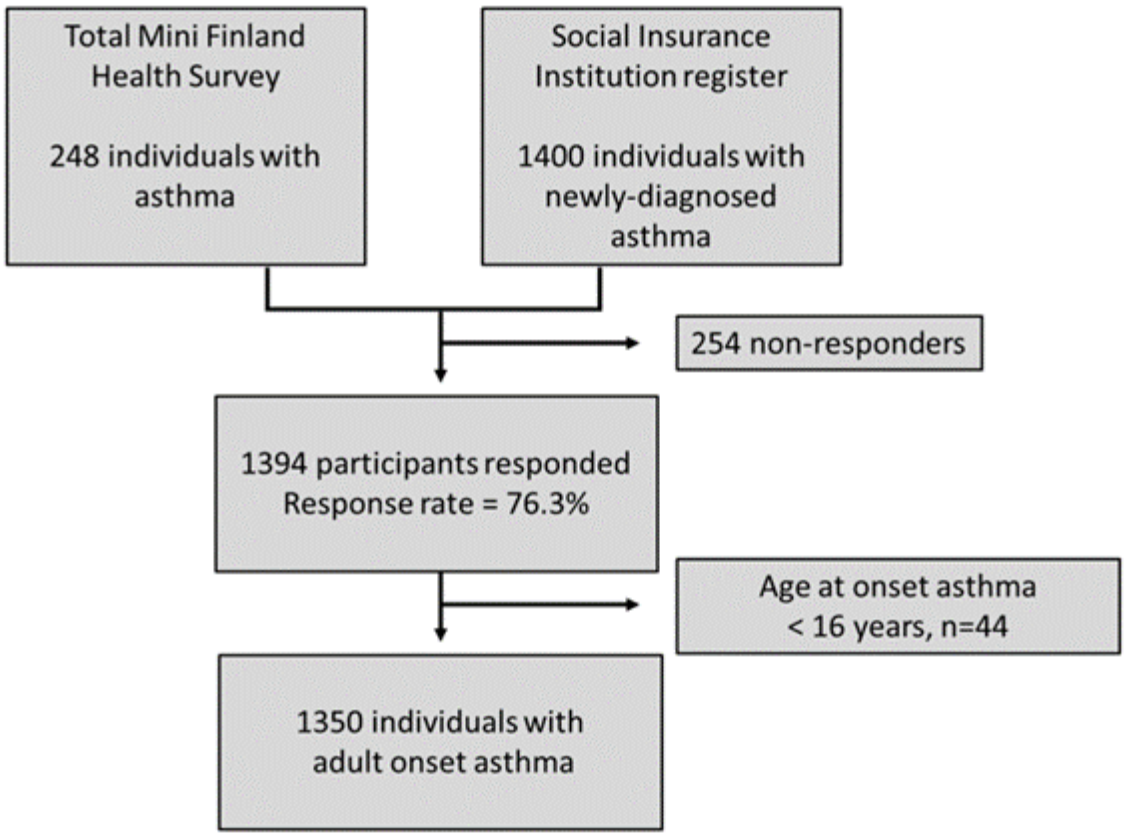

Figure 1

Flow chart of the study population. Asthmatics drawn from the Finnish Drug Reimbursement register were over 30 years old. 248 asthmatics were from the longitudinal, population-based Mini Finland Health Survey. 1400 asthmatics had recently (in 2 years) diagnosed asthma. The asthma was defined to be

adult-onset, if the subject responded that the onset of asthma symptoms and/or the age of asthma diagnosis was 16 years or over.

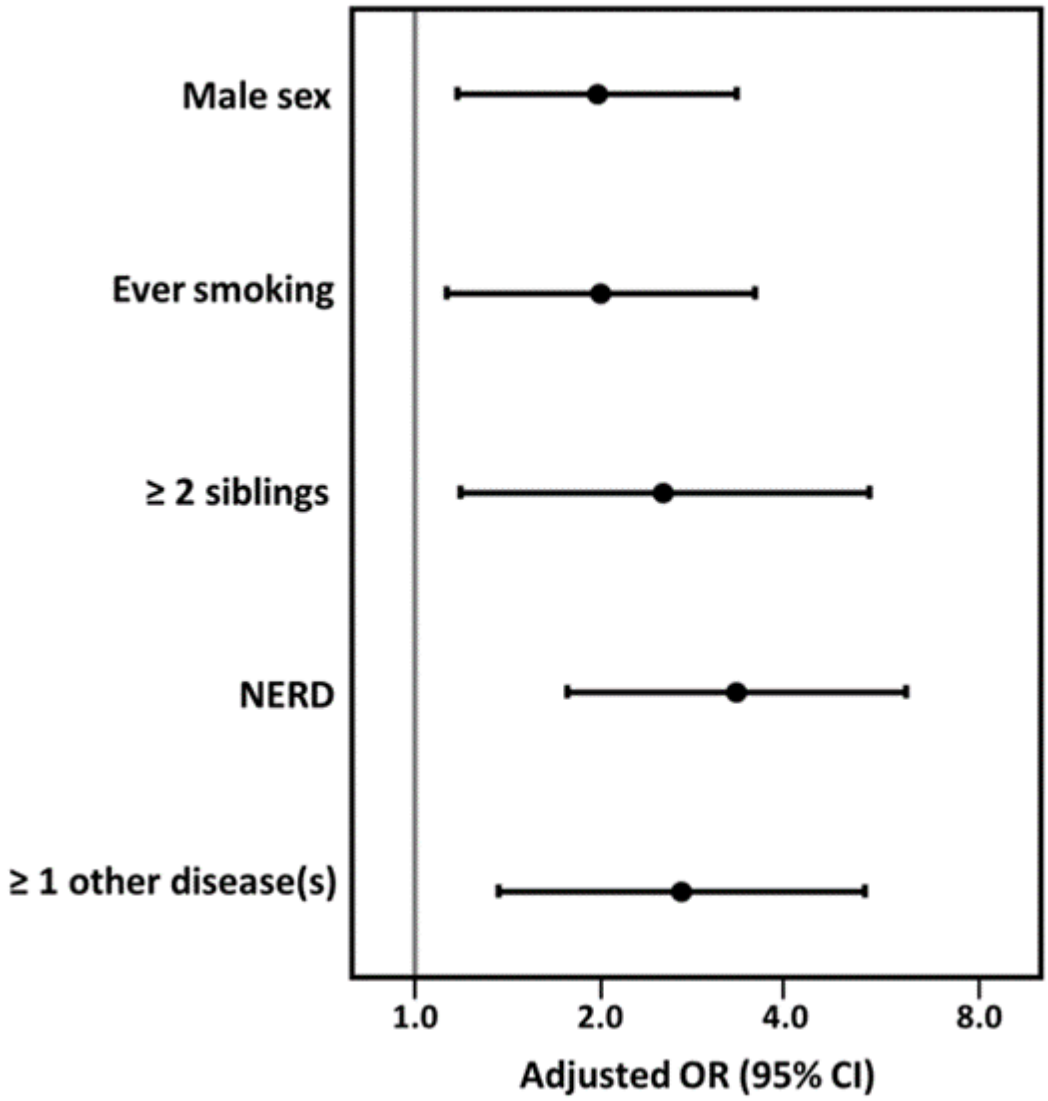

Figure 2

Forest plot summarizing the associations between risk factors and severe adult-onset asthma by using question based definition of severe asthma (Sev-Q). Adjusted OR and 95%CI of severe adult-onset asthma are presented for gender, smoking status, number of siblings, presence of patient-reported NSAID-exacerbated respiratory disease (NERD), and other chronic diseases. Models were adjusted on all these risk factors and age, education, training, severe childhood infection(s)1 and presence of chronic rhinosinusitis with nasal polyps. In this multi-variable model the number of severe asthmatics is 79 and non-severe asthmatics is 1094. 1pneumonia before or during school age and/or hospitalization due to infection at ≤3 years of age. Education level = baccalaureate/secondary vs. primary school; professional training = completed professional college/university/ courses/completed trade school vs. no. OR = odds ratio. CI= confidence interval. Severe asthma (Sev-Q) was defined as self-reported severe asthma AND

asthma symptoms causing much harm AND regular impairment AND (≥1 oral corticosteroid course/year or regular oral corticosteroids AND/OR wake up in the night due to asthma symptoms/wheezing attach ≥ a few times/month).