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Rhinitis phenotypes correlate with different symptom presentation and risk factor patterns of asthma

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Summary
Background: Asthma and rhinitis frequently coexist, but no population study has previously determined the relationship between nasal comorbidities and symptom expression and risk factors of asthma.
Methods: In 2008, a postal questionnaire on respiratory health was sent to 30 000 randomly selected subjects aged 16–75 years in West Sweden; 29218 could be traced and 18 087 (62%) responded. The questionnaire included questions on asthma, rhinitis, chronic rhinosinusitis, respiratory symptoms and possible determinants.
Results: Prevalence of allergic rhinitis in asthma was 63.9% and of asthma in allergic rhinitis 19.8%. Prevalence of chronic rhinosinusitis in asthma was 8.4% and of asthma in chronic rhinosinusitis 24.4%. Asthma subjects with chronic rhinitis, or chronic rhinosinusitis, had more symptoms of asthma and bronchitis than those without rhinitis ($p < 0.001$). There was an obvious trend of higher ORs for various environmental exposures including occupational exposure to dust, gases and fumes (OR 2.32 *vs.* OR 1.44), visible mould at home (OR 1.72 *vs.* OR 1.27) and water damage at home (OR 1.82 *vs.* OR 1.06) for asthma with chronic rhinosinusitis than for asthma with allergic rhinitis. Family history of allergy yielded a higher OR for asthma with allergic rhinitis than with asthma with chronic rhinosinusitis (OR 7.15 *vs.* OR 4.48).

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Conclusion: Considerable overlap between asthma and nasal comorbidities was documented, confirming a close relationship between nasal disease and asthma. Allergic rhinitis, chronic rhinitis and chronic rhinosinusitis were associated with different risk factor patterns and symptom expression of asthma. Thus, different nasal comorbidities may reflect different phenotypes of asthma.

Introduction

Asthma and rhinitis are common chronic disorders with an estimated 700 million sufferers worldwide.[1] Both asthma and rhinitis are considered syndromes with a number of clinical phenotypes,[2,3] as well as biological endotypes.[4] The conditions frequently coexist, both in atopic and non-atopic individuals.[5] Rhinitis is further considered an important risk factor for developing asthma.[6,7] Concomitant rhinitis appears to impair asthma control,[8] whereas adequate treatment of allergic rhinitis seems to be beneficial also for asthma.[9–11]

While a number of population-based studies have investigated the association between asthma and allergic rhinitis,[12–15] studies on the correlation between asthma and chronic nasal symptoms are few.[15–17] Studies from otolaryngology and asthma clinics have suggested considerable comorbidity between asthma and chronic rhinosinusitis.[17] However, mainly due to previous lack of consensus in the definition of chronic rhinosinusitis, population-based studies are few. There are at present no published population-based studies on comorbidity of asthma and chronic rhinosinusitis.

The genetic component of asthma and rhinitis is considered to be of great importance.[18] Even so, a number of environmental risk factors, including occupational exposure to irritant factors and home dampness, have been associated with the conditions.[18–21] Although various studies have presented risk factors for asthma and rhinitis separately,[7,12,19–23] to the authors' knowledge, no previous study has presented risk factors for asthma with different nasal comorbidities.

The aim of this study was to investigate the prevalence of asthma and lower respiratory symptoms in subjects with allergic rhinitis, chronic rhinitis and chronic rhinosinusitis and *vice versa* (i), how the expression of lower respiratory symptoms in asthma subjects varies with different nasal comorbidities (ii) and what the risk factors are for asthma with different nasal comorbidities (iii).

Methods

Study population

In 2008, a self-administered questionnaire was mailed with three reminders to 30 000 inhabitants in West Sweden, aged 16–75 years. By computerised randomisation 15 000 subjects were selected from the urbanised area of Gothenburg. Similarly, a random sample of 15 000 subjects of the same age was selected from the rest of the region. Names and addresses were provided by the Swedish Population Register. The invited individuals were given the possibility to respond either by mail or over the internet. Of the 29 218 subjects that were traceable, 18 087 (62%) participated.[22,23] A study of none- and late-response has confirmed the representativeness of the study sample for the population in the studied areas.[24]

Questionnaire

The study questionnaire consisted of the Swedish OLIN study questionnaire,[25] with additional questions about smoking and occupational and environmental exposures, and the Swedish version of the GA^{2}LEN questionnaire.[2] The OLIN questionnaire has been used in several large scale studies in northern Europe and other parts of the world and contains questions about obstructive respiratory diseases, rhinitis, respiratory and nasal symptoms and possible determinants of disease, such as smoking habits and family history of asthma and allergy.[12,22–30]

Definitions

Asthma

As the diagnosis of asthma is arbitrary, three different definitions of asthma were used: report of having ever had asthma *(ever asthma)*, *physician-diagnosed asthma* and *current asthma*. Current asthma was defined as ever asthma or physician-diagnosed asthma *and* at least one out of: current use of asthma medication, attacks of shortness of breath, any wheeze, and recurrent wheeze.

Rhinitis

Allergic rhinitis was defined as having ever had allergic eye or nose problems including hay fever, while *chronic rhinitis* was defined as having either *runny nose* or *nasal congestion* more or less constantly. *Chronic rhinosinusitis* was defined as at least three of the following symptoms: nasal blockage, mucus discharge, facial pain or pressure and reduction of smell, for more than 12 weeks during the past 12 months.

Lower respiratory symptoms

Waking with tight chest was defined as having woken up with a sensation of chest tightness. *Dyspnoea grade 3* was defined as necessity to walk slower than contemporaries on level ground because of breathlessness, following the definition from the Medical Research Council Dyspnoea Index. All other lower respiratory symptoms have been defined elsewhere.[22]

Family history

Family history of asthma was defined as a positive answer to the question: 'Has any of your parents or siblings ever had

asthma', and *family history of allergic rhinitis* was defined as a positive answer to the question: 'Has any of your parents or siblings ever had eye or nose problems (hay fever)'.

Exposures

Current smokers reported smoking during the year preceding the survey, and were classed as *light-moderate smokers* if they smoke less than 15 cigarettes per day and *heavy smokers* if they smoke 15 cigarettes per day or more; *Ex-smokers* reported having stopped smoking at least 12 months preceding the survey; *Non-smokers* reported neither smoking nor ex-smoking. *Occupational exposure* was defined as having been substantially exposed to dust, gases or fumes at work. *Visible mould at home* and *water damage at home* were defined as suffering from any such incidence during the past 10 years. *Farm childhood* was defined as having lived on a farm during your first five years of life. Classes of *level of education* were: completion of *primary school*, *secondary school* or *higher education* (under-graduate, graduate and post-graduate). *Degrees of urbanisation* were categorised based on the number of inhabitants in the localities of residence. Metropolitan *Gothenburg*, with approximately 700 000 inhabitants, was used as a separate entity, while other localities with more than 10 000 inhabitants were considered *mid-size towns* (all with less than 100 000 inhabitants). Localities with 500 to 10 000 inhabitants were considered *small towns* and those with less than 500 inhabitants *rural areas*. The classification was performed by matching the subjects' address information with official population data from Statistics Sweden.[31]

Analyses

Statistical analyses were performed using SPSS version 17.0 (Chicago, IL, USA). Comparisons of proportions were tested with two-sided Fisher's exact test. Linear-by-linear association chi square test was used for testing for trends. A *p*-value of <0.05 was regarded as statistically significant. Multiple logistic regression analysis was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) separately for each of physician-diagnosed asthma, asthma with allergic rhinitis, asthma with chronic rhinitis, asthma with chronic rhinosinusitis and asthma without rhinitis. Independent variables were age, sex, family history of asthma, family history of allergic rhinitis, smoking, water damage at home, visible mould at home, occupational exposure to gas, dust or fumes, farm childhood, level of education and degree of urbanisation. Interaction analyses were performed using the combined variable method assessing interactions between occupational exposure to gas, dust or fumes and smoking, smoking and sex as well as age and all independent variables included in the multivariate analyses.

Results

Asthma in rhinitis

Physician-diagnosed asthma was found to overlap substantially with allergic rhinitis, chronic rhinitis and chronic rhinosinusitis, respectively, as is presented in Venn-diagrams (Fig. 1a and b). Of subjects with physician-diagnosed asthma, 63.9% had allergic rhinitis, 39.8% had chronic rhinitis and 8.4% had chronic rhinosinusitis. Of subjects with chronic rhinosinusitis, 82.7% had chronic rhinitis and 54.0% had allergic rhinitis. Prevalence of ever asthma, physician-diagnosed asthma, current asthma and current use of asthma medication was considerably ($p < 0.001$) higher in subjects with allergic rhinitis, chronic rhinitis and chronic rhinosinusitis, respectively, than in subjects without rhinitis or rhinosinusitis (Table 1). Prevalence of current asthma was studied in relation to combinations of allergic rhinitis, nasal congestion and runny nose (Fig. 2). The prevalence of current asthma increased with the number of nasal conditions, 2.8% in no nasal condition *vs.* 28.5% in three nasal conditions.

Rhinitis in asthma

The prevalence of allergic rhinitis, chronic rhinitis and chronic rhinosinusitis, respectively, increased with increasing occurrence of symptoms common in asthma

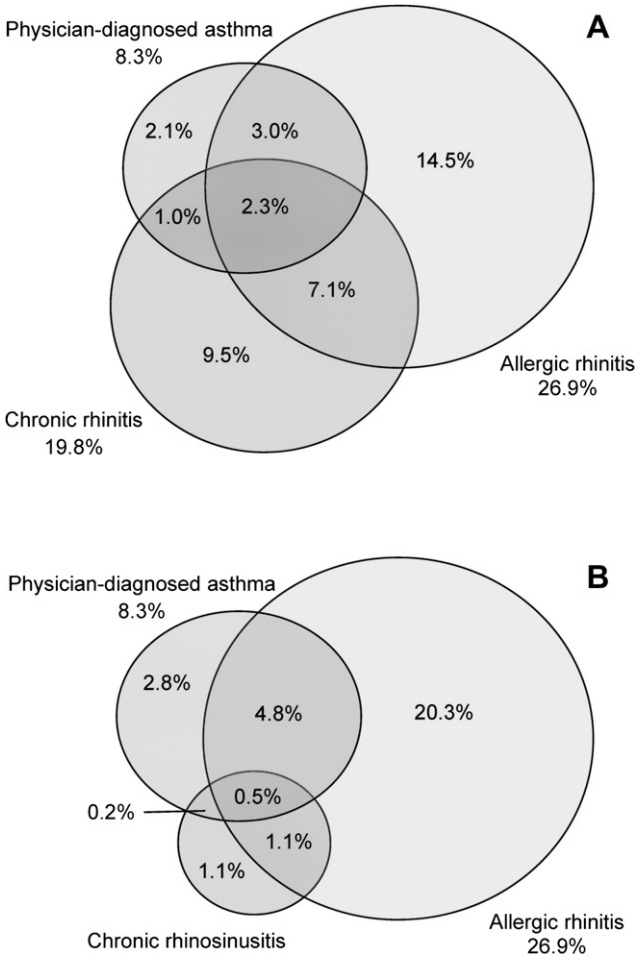

Figure 1 Venn-diagrams of prevalence of (A) physician-diagnosed asthma, allergic rhinitis and chronic rhinitis and (B) physician-diagnosed asthma, allergic rhinitis and chronic rhinosinusitis.

Table 1 Prevalence (%) of different asthma variables in general population and among subjects with *allergic rhinitis, chronic rhinitis* and *chronic rhinosinusitis*, respectively.

Symptom or condition	Prevalence in general population[a]	Allergic rhinitis	Chronic rhinitis	Chronic rhinosinusitis	Free from rhinitis[b]
	(n = 18087)	(n = 4859)	(n = 3586)	(n = 533)	(n = 11213)
Ever asthma	9.7	23.6	19.0	28.5	3.7
Physician-diagnosed asthma	8.3	19.8	16.5	24.4	3.3
Current asthma	8.1	20.2	17.7	26.8	2.7
Current use of asthma medication	8.6	20.5	18.2	27.8	3.2

[a] Lötvall et al.[23]
[b] Subjects without allergic rhinitis, chronic rhinitis and chronic rhinosinusitis.

(Fig. 3). Allergic rhinitis was reported by 21.3% of subjects without symptoms common in asthma and by 62.6% of subjects with four symptoms common in asthma. Similarly, chronic rhinitis was reported by 14.8% of subjects without symptoms common in asthma and by 55.4% of subjects with four symptoms common in asthma. Chronic rhinosinusitis was tenfold more common in subjects with four symptoms common in asthma than among subjects without symptoms common in asthma (16.0% *vs.* 1.5%, $p < 0.001$).

Nasal comorbidities and symptom expression of asthma

Asthma subjects with allergic rhinitis reported substantially more symptoms common in asthma, including attacks of shortness of breath and any wheeze, than those without allergic rhinitis ($p < 0.001$) (Table 2). In asthma subjects with chronic rhinitis, both symptoms common in asthma and symptoms of bronchitis were more frequent. The pattern found in asthma subjects with chronic rhinitis was present also in those with chronic rhinosinusitis, where prevalence was even higher (Table 2).

The proportion of subjects with no, one, two, three or four symptoms common in asthma among asthma subjects with different nasal comorbidities was analysed (Online supplementary Fig. 1). The proportion of subjects with three symptoms or more was significantly greater in asthma subjects with chronic rhinitis and chronic rhinosinusitis, respectively, than in asthma subjects without these conditions. Indeed, 66% of asthma subjects with chronic rhinosinusitis reported at least three symptoms.

Risk factors for asthma with nasal comorbidities

Large differences were found in the distribution of demographic and other background variables among asthma subjects with different nasal comorbidities (Table 3). Asthma subjects with allergic rhinitis were significantly younger, younger at asthma diagnosis, more commonly reporting a family history of asthma and allergy, respectively, and had a higher level of education than asthma subjects without allergic rhinitis. Asthma subjects with chronic rhinitis reported also more commonly a family history of asthma and allergy, respectively, but were less highly educated than asthma subjects without chronic rhinitis. In addition, asthma subjects with chronic rhinitis reported significantly more of a number of exposures including current smoking, water damage at home, visible mould at home, occupational exposure to dust, gases and fumes and urban living than asthma subjects without

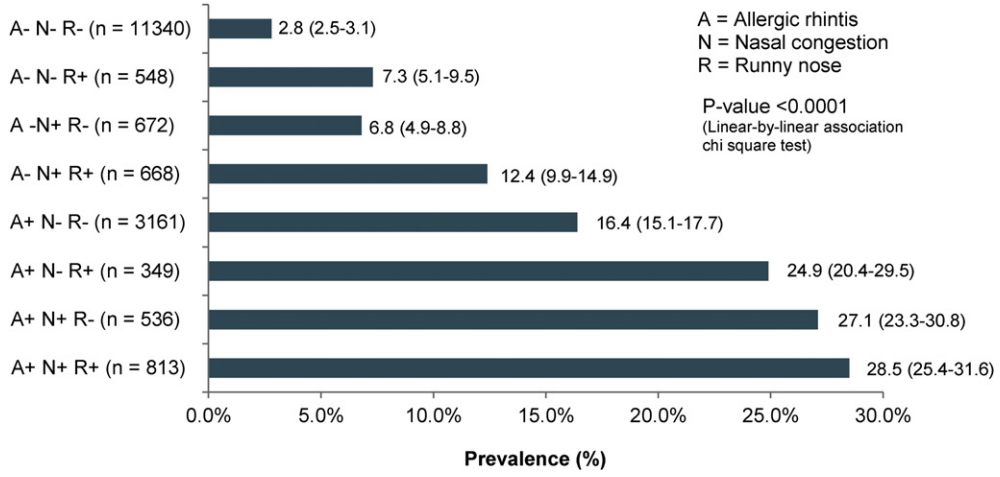

Figure 2 Prevalence of current asthma in relation to allergic rhinitis, nasal congestion and runny nose with 95% confidence intervals. A indicates allergic rhinitis; N nasal congestion; R runny nose; - condition not present; + condition present.

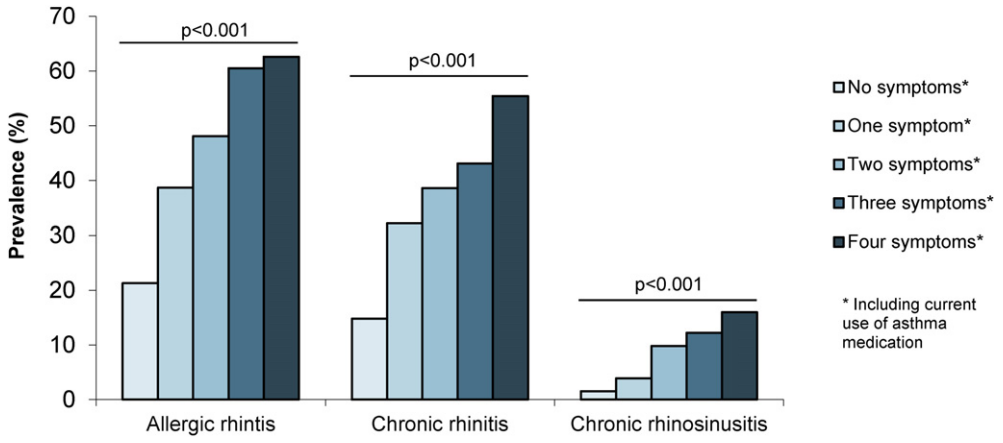

Figure 3 Prevalence of allergic rhinitis, chronic rhinitis and chronic rhinosinusitis among subjects with current asthma medication and symptoms common in asthma. Symptoms were: attacks of shortness of breath, any wheeze and recurrent wheeze.

chronic rhinitis. Asthma subjects with chronic rhinosinusitis had a significantly higher body mass index than asthma subjects without chronic rhinosinusitis. Other significant associations followed, with a few exceptions, those for chronic rhinitis, though the associations with environmental exposures were even stronger in asthma subjects with chronic rhinosinusitis.

Multivariate relationships

Adjusting for the independent variables in Table 4, reporting both family history of asthma and family history of allergic rhinitis was strongly associated with all combinations of asthma and nasal comorbidities, in particular with asthma with allergic rhinitis (OR 7.15; 95% CI

Table 2 Prevalence (%) of respiratory symptoms and conditions in the general population and among subjects having physician-diagnosed asthma with comorbid *allergic rhinitis*, *chronic rhinitis* and *chronic rhinosinusitis*, respectively. Difference (*p*-value) by presence or absence of nasal condition, given in detail in a foot-note below the table.

Symptom or condition	Prevalence in general population[a]	All asthma	p-value[c]	Asthma with allergic rhinitis	p-value[d]	Asthma with chronic rhinitis	p-value[e]	Asthma with chronic rhinosinusitis	p-value[f]	Asthma free from rhinitis[b]	p-value[g]
Attacks of SOB	9.5	60.2	<0.001	64.2	<0.001	68.7	<0.001	75.4	<0.001	47.0	<0.001
Current use of asthma medication	8.6	69.4	<0.001	72.9	<0.001	75.8	<0.001	78.5	0.017	58.2	<0.001
Any wheeze	16.6	61.1	<0.001	65.0	<0.001	71.6	<0.001	79.2	<0.001	49.2	<0.001
Waking with tight chest	9.1	32.4	<0.001	35.3	0.001	42.1	<0.001	60.0	<0.001	22.3	<0.001
Recurrent wheeze	6.8	32.2	<0.001	32.2	0.95	45.7	<0.001	52.3	<0.001	24.2	<0.001
Longstanding cough	11.4	29.7	<0.001	29.8	0.91	37.9	<0.001	50.8	<0.001	22.6	<0.001
Sputum production	13.3	39.1	<0.001	39.2	0.96	55.2	<0.001	66.9	<0.001	29.3	<0.001
Chronic productive cough	6.1	20.6	<0.001	19.5	0.15	30.8	<0.001	44.6	<0.001	16.8	0.038
Dyspnoea grade 3 (MRC dyspnoea index)	6.6	21.2	<0.001	19.3	0.018	28.4	<0.001	42.3	<0.001	20.7	0.83

[a] Lötvall et al.[23]
[b] Subjects without allergic rhinitis, chronic rhinitis and chronic rhinosinusitis.
[c] Asthma vs. not asthma.
[d] Asthma with allergic rhinitis vs. asthma without allergic rhinitis.
[e] Asthma with chronic rhinitis vs. asthma without chronic rhinitis.
[f] Asthma with chronic rhinosinusitis vs. asthma without chronic rhinosinusitis.
[g] Asthma free from rhinitis vs. asthma with any rhinitis.

Table 3 Characteristics of physician-diagnosed asthma with comorbid *allergic rhinitis*, *chronic rhinitis* and *chronic rhinosinusitis*, respectively. Difference (*p*-value) by presence or absence of nasal condition.

Symptom or condition	General population	All asthma	p-value[a]	Asthma with allergic rhinitis	p-value[b]	Asthma with chronic rhinitis	p-value[c]	Asthma with chronic rhinosinusitis	p-value[d]
Mean age (years, SD)	45.3 (±16.2)	43.4 (±16.1)	<0.001	41.6 (±15.0)	<0.001	42.7 (±16.1)	0.14	44.3 (±14.2)	0.45
Mean body mass index (SD)	25.1 (±4.3)	25.9 (±5.0)	<0.001	25.7 (±5.1)	0.14	26.3 (±5.2)	0.011	27.5 (±6.4)	<0.001
Mean age (years) of asthma diagnosis (SD)	21.9 (±18.0)	22.0 (±18.1)	0.51	20.3 (±16.8)	<0.001	22.9 (±18.5)	0.47	24.3 (±18.2)	0.20
Female gender (%)	54.7	60.0	<0.001	60.0	1.00	62.1	0.20	67.7	0.075
Family history of asthma (%)	18.0	39.5	<0.001	43.1	<0.001	43.2	0.021	43.4	0.38
Family history of allergy (%)	28.7	50.2	<0.001	62.7	<0.001	56.0	<0.001	59.0	0.053
Level of education: primary (%)	38.9	20.8	0.13	17.0	<0.001	21.0	0.90	20.8	1.00
secondary (%)	38.4	39.3	0.18	39.2	0.91	43.3	0.011	47.7	0.049
higher (%)	22.8	38.1	0.96	42.4	<0.001	34.0	0.009	29.2	0.030
Current smoking (%)	16.8	16.7	1.00	15.5	0.105	18.3	0.22	28.0	0.001
Water damage at home (%)	13.2	15.2	0.022	16.0	0.26	18.6	0.003	24.8	0.003
Visible mould at home (%)	8.2	11.4	<0.001	12.0	0.31	13.7	0.030	18.8	0.012
Occupational exposure to dust, gases or fumes (%)	22.2	28.3	<0.001	28.6	0.81	35.7	<0.001	42.3	<0.001
Farm childhood (%)	14.3	11.7	0.002	11.5	0.8	12.3	0.56	15.5	0.15
Urban living (>10 000 inh.) (%)	68.5	67.6	0.45	68.5	0.33	71.2	0.018	73.1	0.17

[a] Asthma vs. not asthma.
[b] Asthma with allergic rhinitis *vs.* asthma without allergic rhinitis.
[c] Asthma with chronic rhinitis vs. asthma without chronic rhinitis.
[d] Asthma with chronic rhinosinusitis vs. asthma without chronic rhinosinusitis.

Table 4 Risk factors (OR and 95% confidence interval, CI) for physician-diagnosed asthma, asthma with allergic rhinitis, asthma with chronic rhinitis, asthma with chronic rhinosinusitis and asthma without rhinitis by multiple logistic regression analysis. Statistically significant associations are presented in bold figures.

Independent variables		Dependent variables				
Variables	Categories	All asthma	Asthma with allergic rhinitis	Asthma with chronic rhinitis	Asthma with chronic rhinosinusitis	Asthma free from rhinitis[b]
		OR[a] (95% CI)	OR[a] (95% CI)	OR[a] (95% CI)	OR[a] (95% CI)	OR[a] (95% CI)
Sex	Women (reference: men)	**1.19 (1.05–1.34)**	1.13 (0.98–1.31)	**1.32 (1.10–1.59)**	**1.69 (1.12–2.55)**	1.18 (0.94–1.48)
Family history	Asthma	**2.13 (1.71–2.64)**	**1.87 (1.37–2.55)**	**1.95 (1.36–2.78)**	0.96 (0.35–2.68)	**2.23 (1.59–3.14)**
	Allergic rhinitis	**1.74 (1.49–2.02)**	**2.71 (2.26–3.25)**	**1.99 (1.57–2.51)**	**2.04 (1.24–3.34)**	**0.57 (0.40–0.83)**
	Both	**4.34 (3.73–5.04)**	**7.15 (5.99–8.53)**	**4.59 (3.67–5.74)**	**4.48 (2.81–7.15)**	1.17 (0.82–1.67)
Age	61–75 years	1	1	1	1	1
	46–60 years	0.90 (0.75–1.07)	1.05 (0.83–1.33)	0.98 (0.74–1.29)	1.00 (0.55–1.81)	0.80 (0.59–1.10)
	31–45 years	0.99 (0.82–1.19)	1.26 (0.99–1.60)	1.02 (0.76–1.37)	1.15 (0.62–2.11)	0.76 (0.54–1.07)
	16–30 years	1.11 (0.92–1.34)	1.25 (0.97–1.60)	1.18 (0.88–1.60)	0.61 (0.30–1.22)	1.05 (0.74–1.49)
Level of education	Primary education	1	1	1	1	1
	Secondary education	0.98 (0.83–1.16)	1.04 (0.84–1.30)	0.98 (0.76–1.37)	1.43 (0.83–2.47)	0.89 (0.66–1.20)
	Higher education	0.97 (0.82–1.15)	1.15 (0.92–1.43)	0.81 (0.62–1.05)	0.84 (0.46–1.53)	0.83 (0.61–1.14)
Smoking	Non smoker	1	1	1	1	1
	Ex-smoker	**1.29 (1.12–1.48)**	**1.33 (1.12–1.58)**	**1.28 (1.03–1.58)**	1.18 (0.74–1.90)	1.23 (0.94–1.60)
	Light-moderate smoker	0.93 (0.77–1.12)	0.90 (0.71–1.13)	0.92 (0.70–1.22)	1.30 (0.74–2.26)	1.03 (0.73–1.45)
	Heavy smoker	0.97 (0.82–1.31)	0.88 (0.60–1.29)	1.01 (0.65–1.57)	1.97 (0.97–3.98)	1.07 (0.61–1.87)
Degree of urbanisation	Rural areas (<500 inh.)	1	1	1	1	1
	Small towns (500 – 10000 inh.)	1.10 (0.90–1.35)	1.09 (0.84–1.41)	1.05 (0.75–1.47)	1.14 (0.55–2.36)	1.07 (0.74–1.55)
	Mid-sized towns (>10 000 inh.)	0.96 (0.78–1.17)	1.00 (0.78–1.29)	1.23 (0.90–1.68)	1.45 (0.74–2.84)	0.74 (0.50–1.07)
	Gothenburg (700 000 inh.)	0.88 (0.99–1.19)	0.99 (0.79–1.25)	1.20 (0.90–1.61)	1.41 (0.75–2.65)	0.87 (0.62–1.22)
Water damage at home	Yes (reference: no)	1.02 (0.86–1.21)	1.06 (0.87–1.30)	1.27 (1.00–1.62)	**1.82 (1.14–2.90)**	0.78 (0.55–1.10)
Visible mould	Yes (reference: no)	**1.29 (1.06–1.57)**	**1.27 (1.01–1.61)**	**1.34 (1.01–1.78)**	**1.72 (1.02–2.94)**	1.23 (0.85–1.80)
Occupational exposure	Yes (reference: no)	**1.43 (1.25–1.64)**	**1.44 (1.22–1.70)**	**1.94 (1.59–2.35)**	**2.32 (1.54–3.48)**	**1.34 (1.04–1.71)**
Farm childhood	Yes (reference: no)	**0.81 (0.67–0.97)**	0.90 (0.71–1.12)	0.91 (0.69–1.20)	1.34 (0.79–2.27)	0.80 (0.58–1.10)

[a] Adjusted for all listed independent variables.
[b] Asthma subjects without allergic rhinitis, chronic rhinitis and chronic rhinosinusitis.

5.99—8.53). Occupational exposure to gas, dust and fumes yielded higher ORs for asthma with chronic rhinosinusitis (OR 2.32; 95% CI 1.54—3.48) and chronic rhinitis (OR 1.94; 95% CI 1.59—2.35), respectively, than for asthma with allergic rhinitis (OR 1.44; 95% CI 1.22—1.70). Visible mould at home was significantly associated with all combinations of asthma and nasal comorbidities (OR 1.27—1.72), whereas water damage at home was associated only with asthma with chronic rhinosinusitis (OR 1.82; 95% CI 1.14—2.90). Ex-smoking was a weak but statistically significant risk factor for asthma with allergic rhinitis (OR 1.33; 95% CI 1.12—1.58) and asthma with chronic rhinitis (OR 1.28; 95% CI 1.03—1.58). Heavy smoking yielded a high OR, 1.97, for asthma with chronic rhinosinusitis, but confidence intervals were wide. Female gender was associated with asthma with chronic rhinitis (OR 1.32; 95% CI 1.10—1.59) and chronic rhinosinusitis (OR 1.69; 95% CI 1.12—2.55), but not asthma with allergic rhinitis.

Several interaction analyses were performed and a number of additive effects between risk factors of asthma and rhinitis were found. The interactions between occupational exposure and smoking (A) and that between smoking and gender (B) on the risk for asthma with chronic rhinosinusitis are presented in Fig. 4. Some risk factors of asthma and rhinitis were age dependent (Table 5). Farm childhood was a protective factor for physician-diagnosed asthma in young adults, but not in middle age or elderly. Interestingly, the same exposure was a risk factor for asthma with chronic rhinosinusitis in young adults, however not in middle aged or elderly.

Discussion

Extensive comorbidity was found between asthma, allergic rhinitis, chronic rhinitis and chronic rhinosinusitis. Prevalence of asthma increased with increasing number of nasal symptoms, and prevalence of all nasal comorbidities increased with increasing lower respiratory symptoms, all in a dose—response manner. Furthermore, the symptom expression and risk factor pattern of asthma differed considerably between asthma subjects with allergic rhinitis, chronic rhinitis, chronic rhinosinusitis and those free from rhinitis, suggesting that nasal comorbidities may be markers of different disease phenotypes of asthma. All this adds to the knowledge about the link between asthma and rhinitis.

Population-based studies on the comorbidity of asthma and rhinitis are few,[12—16] and most of them focus on asthma and allergic rhinitis without considering upper and lower respiratory symptoms. In the current study, prevalence of allergic rhinitis in asthma was 64% and prevalence of asthma in allergic rhinitis 20%. These findings are well in agreement with results from a large European multi-centre study[13] which found a prevalence of rhinitis in asthma of 50—77% and of asthma in rhinitis of 8—23%. We found considerable overlap also between asthma and chronic rhinitis, which is consistent with previous findings.[16]

There are no previous published population-based studies on the comorbidity of asthma and chronic rhinosinusitis. Some clinical studies have suggested that >50% of patients with chronic rhinosinusitis have comorbid asthma.[17] We found that 24% of subjects with chronic rhinosinusitis had physician-diagnosed asthma. Our result is in line with a Belgian study on a small selection of patients with chronic rhinosinusitis, using objective methods in assessing chronic rhinosinusitis and asthma, which demonstrated comorbid asthma also in 24% of patients with chronic rhinosinusitis.[32] Sinonasal symptoms are frequently reported in asthma patients,[33,34] and in severe asthmatics 24% has been found to have extensive sinus disease.[33] We found that in unselected asthma subjects including mild asthma from the general population, 8.4% had comorbid chronic rhinosinusitis.

There is a common clinical observation that nasal comorbidities are associated not only with prevalence of asthma, but also with disease severity.[34,35] Asthma severity is difficult to measure in questionnaire studies, but the burden of lower respiratory symptoms could serve as a proxy for severity. We found that asthma subjects with chronic rhinosinusitis reported considerably more lower respiratory symptoms than those with allergic rhinitis as well as those without nasal comorbidities.

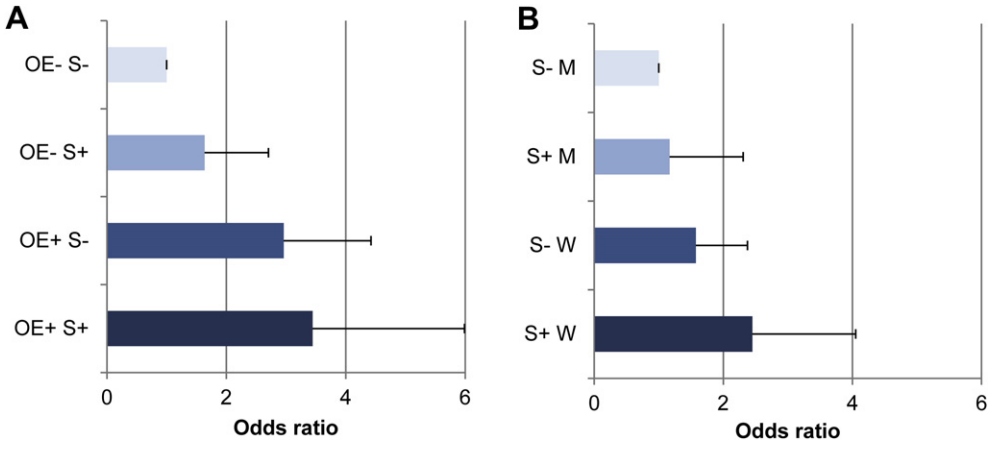

Figure 4 Risk of asthma with chronic rhinosinusitis depending on A: occupational exposure (OE) and smoking (S) and B: smoking (S) and sex (W = women; M = men). + = exposure present; - = exposure absent. OR and 95% CI with unexposed non-smokers (A) and non-smoking men (B), respectively, as reference = 1. All odds ratios were also adjusted for age, visible mould at home, water damage at home, farm childhood, degree of urbanisation and level of education.

Table 5 Age dependent risk (OR and 95% confidence interval, CI) for physician-diagnosed asthma, asthma with allergic rhinitis and asthma with chronic rhinosinusitis by multiple logistic regression analysis. Statistically significant associations are presented in bold figures.

		All asthma	Asthma with allergic rhinitis	Asthma with chronic rhinosinusitis
		OR[a] (95% CI)	OR[a] (95% CI)	OR[a] (95% CI)
Age and farm childhood (F)	**Farm- 16–45 years**	**1.38 (1.02–1.89)**	1.40 (0.96–2.04)	**0.46 (0.22–0.96)**
	Farm+ 16–45 years	**0.72 (0.53–0.98)**	0.71 (0.49–1.04)	**2.15 (1.04–4.45)**
	Farm- 46–75 years	1.14 (0.91–1.43)	0.93 (0.70–1.25)	1.17 (0.56–2.48)
	Farm+ 46-75 years	0.88 (0.70–1.10)	1.07 (0.80–1.43)	0.85 (0.40–1.79)
Age and occupational exposure (OE)	**OE- 16-45 years**	**0.81 (0.68–0.97)**	0.82 (0.67–1.02)	0.69 (0.39–1.22)
	OE+ 16–45 years	**1.23 (1.03–1.48)**	1.21 (0.98–1.50)	1.44 (0.82–2.55)
	OE- 46-75 years	**0.59 (0.49–0.72)**	**0.53 (0.41–0.69)**	**0.22 (0.12–0.41)**
	OE+ 46–75 years	**1.69 (1.38-2.05)**	**1.87 (1.44–2.42)**	**4.50 (2.46–8.24)**
Age and sex (M = men; W = women)	**M 16–45 years**	0.90 (0.77–1.05)	1.01 (0.84–1.21)	**0.56 (0.32–0.97)**
	W 16–45 years	1.11 (0.95–1.30)	0.99 (0.82–1.19)	**1.80 (1.03–3.14)**
	M 46–75 years	**0.76 (0.63–0.91)**	**0.70 (0.55–0.89)**	0.58 (0.31–1.07)
	W 46–75 years	**1.32 (1.10–1.59)**	**1.44 (1.12–1.83)**	1.73 (0.94–3.19)
Age and ex-smoking (ES)	**ES- 16–45 years**	0.89 (0.72–1.10)	**0.73 (0.58–0.93)**	0.64 (0.34–1.19)
	ES+ 16-45 years	1.13 (0.91–1.39)	**1.37 (1.08–1.74)**	1.57 (0.80–3.07)
	ES- 46–75 years	**0.71 (0.60–0.85)**	**0.73 (0.58–0.92)**	1.23 (0.67–2.28)
	ES+ 46–75 years	**1.41 (1.18–1.68)**	**1.36 (1.08–1.72)**	0.81 (0.44–1.50)

[a] Adjusted for farm childhood, occupational exposure, sex, ex-smoking, water damage at home, visible mould at home, degree of urbanisation, level of education, family history of asthma and family history of allergy.

Data on the symptom expression of asthma with different nasal comorbidities has not been published or studied previously. We found that asthma subjects with comorbid allergic rhinitis had a higher prevalence of symptoms common in asthma, but not symptoms of bronchitis, whereas asthma subjects with chronic rhinitis and chronic rhinosinusitis, respectively, had a considerably higher prevalence of all investigated respiratory symptoms. Consistently, asthma subjects without rhinitis reported considerably less respiratory symptoms. Thus, we identified the presence of chronic nasal symptoms as a marker for a highly symptomatic phenotype of asthma, including both symptoms common in asthma and symptoms of bronchitis.

In previous studies we have presented risk factors for allergic rhinitis and asthma separately.[22,23] In the present study, we calculated risk factors for combinations of asthma and rhinitis. As was found for asthma,[22] family history of asthma was a strong risk factor for comorbid asthma and rhinitis. Furthermore, female gender was associated with a higher risk of asthma with chronic rhinitis and chronic rhinosinusitis, but not asthma with allergic rhinitis. In agreement with studies on asthma,[12,29,36] ex-smoking was a risk factor for asthma with comorbid rhinitis. However, farm childhood and degree of urbanisation were not associated with combined asthma and rhinitis, in contrast to what was found for allergic rhinitis[23] and in asthma in the adolescence.[28] Associations with a number of environmental exposures including occupational exposure to dust, gases and fumes, visible mould at home, water damage at home and current smoking were apparently stronger for asthma with chronic rhinosinusitis than for other asthma outcomes. However, the size of the group with chronic rhinosinusitis and asthma was small and all associations did not reach significance in the multiple regression model.

Interaction analyses yielded a number of additive effects between risk factors of asthma and rhinitis and various risk factors were age dependent. In the young, farm childhood was a risk factor for asthma with chronic rhinosinusitis and a protective factor for physician-diagnosed asthma. These findings further support the view of asthma as a syndrome with multiple aetiologies.

The present study benefits from its population-based design, large scale and wide age span. A study of non-response confirmed the study sample as being highly representative for the studied areas.[24] Further strengths are the use of well-defined and validated questions. A consensus in how to define chronic rhinosinusitis in epidemiological research has long been lacking. Our definition of chronic rhinosinusitis was based on the EP^{3}OS recommendations,[17] but we required at a minimum three out of four symptoms in order to avoid extensive overlap with the group of chronic rhinitis. The study was of a cross-sectional design, which means that risk factor analyses need to be interpreted with caution. Other limitations are those inherent in questionnaire-based studies, i.e. the lack of objective measurements. However, preliminary results from an ongoing clinical follow-up confirmed that the great majority of those reporting allergic rhinitis were sensitised to at least one common airborne allergen. Furthermore, almost all (i.e. >99%) subjects with allergic rhinitis also reported current symptoms of rhinitis, confirming the validity of the question. The question on physician-diagnosed

asthma has been confirmed as being highly specific for asthma while sensitivity is somewhat lower.[37,38]

In summary, our results further expand the knowledge about the link between asthma and nasal comorbidities in adults. Symptom characteristics and risk factor patterns of asthma differed substantially with different nasal comorbidities, suggesting that nasal comorbidities may reflect different disease phenotypes of asthma.

Conflict of interests

The authors declare that they have no competing interests.

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Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.rmed.2011.06.004.

References

1. Bousquet J, Dahl R, Khaltaev N. Global alliance against chronic respiratory diseases. *Allergy* 2007;**62**:216—23.
2. Bousquet J, Fokkens W, Burney P, Durham SR, Bachert C, Akdis CA, et al. Important research questions in allergy and related diseases: nonallergic rhinitis: a GA2LEN paper. *Allergy* 2008;**63**:842—53.
3. Wenzel SE. Asthma: defining of the persistent adult phenotypes. *Lancet* 2006;**368**:804—13.
4. Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. *Lancet* 2008;**372**:1107—19.
5. Leynaert B, Bousquet J, Neukirch C, Liard R, Neukirch F. Perennial rhinitis: an independent risk factor for asthma in nonatopic subjects: results from the European community respiratory health survey. *J Allergy Clin Immunol* 1999;**104**:301—4.
6. Shaaban R, Zureik M, Soussan D, Neukirch C, Heinrich J, Sunyer J, et al. Rhinitis and onset of asthma: a longitudinal population-based study. *Lancet* 2008;**372**:1049—57.
7. Torén K, Olin AC, Hellgren J, Hermansson BA. Rhinitis increase the risk for adult-onset asthma—a Swedish population-based case-control study (MAP-study). *Respir Med* 2002;**96**:635—41.
8. Bousquet J, Gaugris S, Kocevar VS, Zhang Q, Yin DD, Polos PG, et al. Increased risk of asthma attacks and emergency visits among asthma patients with allergic rhinitis: a subgroup analysis of the investigation of montelukast as a partner agent for complementary therapy. *Clin Exp Allergy* 2005;**35**:723—7 [corrected].
9. Corren J, Manning BE, Thompson SF, Hennessy S, Strom BL. Rhinitis therapy and the prevention of hospital care for asthma: a case-control study. *J Allergy Clin Immunol* 2004;**113**:415—9.
10. Virchow JC, Bachert C. Efficacy and safety of montelukast in adults with asthma and allergic rhinitis. *Respir Med* 2006;**100**:1952—9.
11. Ribeiro de Andrade C, Chatkin JM, Fiterman J, Scaglia N, Camargos PA. Unified disease, unified management: treating allergic rhinitis and asthma with nasally inhaled corticosteroid. *Respir Med* 2010;**104**:1577—80.
12. Lundbäck B. Epidemiology of rhinitis and asthma. *Clin Exp Allergy* 1998;**28**(Suppl. 2):3—10.
13. Leynaert B, Neukirch C, Kony S, Guenegou A, Bousquet J, Aubier M, et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. *J Allergy Clin Immunol* 2004;**113**:86—93.
14. Leynaert B, Neukirch C, Liard R, Bousquet J, Neukirch F. Quality of life in allergic rhinitis and asthma. A population-based study of young adults. *Am J Respir Crit Care Med* 2000;**162**:1391—6.
15. Bugiani M, Carosso A, Migliore E, Piccioni P, Corsico A, Olivieri M, et al. Allergic rhinitis and asthma comorbidity in a survey of young adults in Italy. *Allergy* 2005;**60**:165—70.
16. Montnémery P, Svensson C, Ädelroth E, Löfdahl CG, Andersson M, Greiff L, et al. Prevalence of nasal symptoms and their relation to self-reported asthma and chronic bronchitis/emphysema. *Eur Respir J* 2001;**17**:596—603.
17. Fokkens W, Lund V, Mullol J. EP3OS 2007: European position paper on rhinosinusitis and nasal polyps 2007. A summary for otorhinolaryngologists. *Rhinology* 2007;**45**:97—101.
18. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic rhinitis and its Impact on asthma (ARIA) 2008 update (in collaboration with the world health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;**63**(Suppl. 86):8—160.
19. Bjerg A, Sandström T, Lundbäck B, Rönmark E. Time trends in asthma and wheeze in Swedish children 1996—2006: prevalence and risk factors by sex. *Allergy* 2010;**65**:48—55.
20. Thorn J, Brisman J, Torén K. Adult-onset asthma is associated with self-reported mold or environmental tobacco smoke exposures in the home. *Allergy* 2001;**56**:287—92.
21. Torén K, Balder B, Brisman J, Lindholm N, Löwhagen O, Palmqvist M, et al. The risk of asthma in relation to occupational exposures: a case-control study from a Swedish city. *Eur Respir J* 1999;**13**:496—501.
22. Lötvall J, Ekerljung L, Rönmark EP, Wennergren G, Lindén A, Rönmark E, et al. West Sweden Asthma Study: prevalence trends over the last 18 years argues no recent increase in asthma. *Respir Res* 2009;**10**:94.
23. Eriksson J, Ekerljung L, Lötvall J, Pullerits T, Wennergren G, Rönmark E, et al. Growing up on a farm leads to lifelong protection against allergic rhinitis. *Allergy* 2010;**65**:1397—403.
24. Rönmark EP, Ekerljung L, Lötvall J, Torén K, Rönmark E, Lundbäck B. Large scale questionnaire survey on respiratory health in Sweden: effects of late- and non-response. *Respir Med* 2009;**103**:1807—15.
25. Lundbäck B, Nyström L, Rosenhall L, Stjernberg N. Obstructive lung disease in northern Sweden: respiratory symptoms assessed in a postal survey. *Eur Respir J* 1991;**4**:257—66.
26. Meren M, Jannus-Pruljan L, Loit HM, Polluste J, Jönsson E, Kiviloog J, et al. Asthma, chronic bronchitis and respiratory symptoms among adults in Estonia according to a postal questionnaire. *Respir Med* 2001;**95**:954—64.
27. Pallasaho P, Lundbäck B, Meren M, Kiviloog J, Loit HM, Larsson K, et al. Prevalence and risk factors for asthma and chronic bronchitis in the capitals Helsinki, Stockholm, and Tallinn. *Respir Med* 2002;**96**:759—69.

28. Wennergren G, Ekerljung L, Alm B, Eriksson J, Lötvall J, Lundbäck B. Asthma in late adolescence—farm childhood is protective and the prevalence increase has levelled off. *Pediatr Allergy Immunol* 2010;**21**:806—13.
29. Rönmark E, Andersson C, Nyström L, Forsberg B, Järvholm B, Lundbäck B. Obesity increases the risk of incident asthma among adults. *Eur Respir J* 2005;**25**:282—8.
30. Lam HT, Rönmark E, Van TTN, Ekerljung L, Kim Chuc NT, Lundbäck B. Increase in asthma and a high prevalence of bronchitis: results from a population study among adults in urban and rural Vietnam. *Respir Med*; 2010.
31. *Population in Swedish localities*; 2005. Available from: http://www.scb.se/statistik/MI/MI0810/2005A01/mi0810tab5.xls [cited 18/11/10].
32. Ragab A, Clement P, Vincken W. Objective assessment of lower airway involvement in chronic rhinosinusitis. *Am J Rhinol* 2004; **18**:15—21.
33. ten Brinke A, Grootendorst DC, Schmidt JT, De Bruine FT, van Buchem MA, Sterk PJ, et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. *J Allergy Clin Immunol* 2002; **109**:621—6.
34. Bresciani M, Paradis L, Des Roches A, Vernhet H, Vachier I, Godard P, et al. Rhinosinusitis in severe asthma. *J Allergy Clin Immunol* 2001;**107**:73—80.
35. Navarro A, Valero A, Julia B, Quirce S. Coexistence of asthma and allergic rhinitis in adult patients attending allergy clinics: ONEAIR study. *J Investig Allergol Clin Immunol* 2008;**18**:233—8.
36. Torén K, Hermansson BA. Incidence rate of adult-onset asthma in relation to age, sex, atopy and smoking: a Swedish population-based study of 15813 adults. *Int J Tuberc Lung Dis* 1999;**3**:192—7.
37. Lundbäck B, Rönmark E, Jönsson E, Larsson K, Sandström T. Incidence of physician-diagnosed asthma in adults—a real incidence or a result of increased awareness? Report from The Obstructive Lung Disease in Northern Sweden Studies. *Respir Med* 2001;**95**:685—92.
38. Torén K, Brisman J, Järvholm B. Asthma and asthma-like symptoms in adults assessed by questionnaires. A literature review. *Chest* 1993;**104**:600—8.