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No further increase of incidence of asthma: Incidence, remission and relapse of adult asthma in Sweden

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KEYWORDS

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Summary

Background: Knowledge about time trends of disease patterns in society is essential for planning and prioritizing health care resources. Longitudinal population-based studies on asthma are scarce but provide an opportunity to assess incidence, remission and relapse of asthma, and their determinants, which were the objectives of the present study.

Methods: A postal questionnaire was sent on two occasions, 1996 and 2006, to a randomly selected sample of subjects aged 20–69 years in 1996. The response rates were 72% and 83%, respectively, and in total 4479 subjects participated in both surveys. The questionnaire included questions on asthma, respiratory symptoms and possible determinants. Logistic regression was used to assess determinants.

Results: Cumulative incidence of asthma was 2.4% (men 1.9%; women 2.8%, $p = 0.06$). Family histories of asthma (OR 2.31, CI 95% 1.42–3.76), rhinitis (OR 2.25, CI 95% 1.43–3.53) and being an ex-smoker (OR 2.17, CI 95% 1.27–3.71) were determinants for incident asthma. The 10-year remission of asthma was 14.6% and inversely associated with rhinitis. Relapse was found in 38% of eligible subjects.

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Conclusions: The current study with high participation rates concludes that the incidence of asthma among adults has been stable in Sweden for the past two decades. Remission was associated with mild disease at study start. Relapse in adults has rarely been reported previously and provide new insight in the course of asthma. Low remission and high relapse further support the view of asthma as a chronic disease; possibly representing fluctuations of the disease over time.

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Introduction

The prevalence of asthma has increased in most parts over the world during the second half of the 20th century. While the prevalence of asthma has been frequently studied studies of the incidence of asthma are still scarce.^{1–7} There is a tendency towards higher incidence rates in more recent studies compared to older studies,⁸ likely indicating an increase in asthma incidence during the last 30–40 years, a result also found in Sweden.⁹ It is, however, not clear whether the increase is still continuing.

The incidence rate varies extensively between different studies, ranging from 0.4 to 11/1000/year.⁵ This discrepancy has several reasons and consideration of the used methods and definitions are of great importance when comparing studies of incidence of asthma. The definition of population at risk is critical for the outcome,^{5,10} and subjects with symptoms common in asthma at the start of the study can be excluded from the population at risk to compensate for changes in diagnostic criteria.^{5,7} When individuals with symptoms at study start have been excluded, similar incidence rates of physician-diagnosed asthma of ~2/1000/year has been reported from the Obstructive Lung Disease in Northern Sweden (OLIN) studies 1986–1996⁵ and the Respiratory Health in Northern Europe study (RHINE) 1990–2000/2002.⁷ Studies without correction for common asthma symptoms at entry report higher incidence rates.^{4,6}

Until recently only a few studies focused on remission of adult asthma based on the general population have been published.^{11–13} As different definitions of remission have been used, the reported remission rates vary, ranging from 0.4 to 2/100 asthmatics/year including results from two recent studies using similar definitions of remission.^{14,15} Only one study has specifically examined remission of respiratory symptoms.¹⁶ To the authors' knowledge only one study of relapse in adult age has been published to date.¹¹

The present study is a 10-year follow-up of a survey performed in the city of Stockholm in 1996 and examined incidence, remission and relapse of adult asthma and their covariates.

Material and methods

Study population

The study started in 1996 when 8000 randomly selected subjects in the city of Stockholm, aged 20–69 years,^{17,18} were identified using the Swedish Population Register which also provided the addresses. Completed answers were received from 5754 subjects (71.9%). A 10-year follow-up was performed among the 5372 (93.4%) subjects who could

be traced in the winter of 2006, using the same method and questions.¹⁸

Methods

The study consisted of a postal self-administered questionnaire. Non-responders received two reminders. The questionnaire was developed from a Swedish questionnaire¹⁹ based mainly on the British MRC questionnaire²⁰ and contained questions on asthma, rhinitis, respiratory symptoms and use of asthma medication. Included symptoms were, among others, recurrent wheeze and attacks of shortness of breath (SOB). Smoking habits, occupation and family history of diseases were also investigated.

Definitions

Ever asthma: "Have you ever had asthma"; *Physician-diagnosed asthma*: "Have you been diagnosed as having asthma by a doctor"; *Asthma medicine*: "Do you currently use asthma medicine (permanently or as needed)"; *Attacks of shortness of breath*: "Do you presently have, or have had in the last 10 years, asthma symptoms (intermittent breathlessness or attacks of shortness of breath; the symptoms may exist simultaneously with or without cough or wheezing)" and "Have you had these problems within the last year"; *Recurrent wheeze*: "Do you usually have wheezing or whistling in your chest when breathing"; *Any wheeze*: "Have you had whistling or wheezing in the chest at any occasion during the last 12 months".

Five smoking categories were defined. *Smokers* reported smoking at both occasions. *Ex-smokers* reported ex-smoking at both occasions. *Starters and restarters* did not smoke or were ex-smokers in 1996 but smokers in 2006. *Quitters* smoked in 1996 but reported ex- or non-smoking in 2006. *Never-smokers* were non-smokers both 1996 and 2006. To be considered as a quitter or an ex-smoker no smoking during the last 12 months was allowed.

Cumulative incidence is the proportion of subjects with no physician-diagnosed asthma at the beginning of the study period which has received an asthma diagnosis at the end of the study. The cumulative incidence of physician-diagnosed asthma was calculated using two populations at risk. *Crude cumulative incidence* was calculated by excluding only subjects reporting physician-diagnosed asthma in 1996 from the population at risk. The population at risk for *adjusted cumulative incidence* excluded also subjects reporting ever asthma, use of asthma medication, attacks of SOB or recurrent wheeze in 1996. The *incidence rate* (*ir*) was assumed to be linear and was estimated using the formula $ir = a / (10 \times (b - (a/2)))$ where *a* is the incident cases and *b* the subjects at risk at the start of the study.

The *remission* of asthma was defined as having physician-diagnosed asthma and at least one of recurrent wheeze, attacks of SOB or use of asthma medication in 1996 but no symptoms or use of asthma medicine during the year preceding the survey in 2006. *Relapse* was defined as physician-diagnosed asthma in 1996 but no wheeze, attacks of SOB or use of asthma medication in the year preceding 1996 and reporting at least one symptom or use of asthma medicine in 2006.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS). The chi-square test was used for bivariate comparisons. Multiple logistic regression analysis was performed for assessment of simultaneous influences of risk factors. Age group, gender, family history of asthma, rhinitis and smoking categories were used as covariates. A p -value <0.05 and a 95% confidence interval were considered significant.

Results

Demographics

Of the 5372 invited subjects, 4479 (83.4%) participated. A majority was still living in the city of Stockholm, while 8.5% had moved but were retained in the study. The response rate was significantly higher among women than men, $p < 0.01$ and among non-smokers compared to smokers, 79% vs. 74%, $p < 0.01$. The highest response rates were observed in the age group of 61–80 years of age. Of the sample, 16.3% stopped smoking during the 10-year study period (Table 2) which comprised 49.4% of the smokers in 1996 (Table 1).

Cumulative incidence and estimated incidence rate

The crude cumulative incidence was calculated by removing the subjects reporting physician-diagnosed asthma in 1996 from the population at risk, the remaining 54 men (2.9%) and 105 women (4.6%) reporting physician-diagnosed asthma in 2006 represent the crude cumulative incidence of 3.8% (Fig. 1). By also removing the subjects reporting ever asthma, use of asthma medication, recurrent wheeze or attacks of SOB in 1996 from the risk population, the adjusted cumulative incidence was calculated at 2.4% (men 1.9%; women 2.8%). A higher crude

Table 2 Smoking categories including changes in smoking habits 1996–2006

Smoking group	Smoking categories 1996–2006					
	Men		Women		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Never-smokers	891	44.5	1102	44.7	1993	44.6
Quitters after 1996	324	16.2	404	16.4	728	16.3
Starters and restarters ^a	53	2.6	59	2.4	112	2.5
Ex-smokers already in 1996	410	20.5	481	19.5	891	19.9
Smokers both in 1996 and 2006	324	16.2	422	17.1	746	16.7
Missing data	2	0.1	4	0.2	6	0.1

^a In the analyses starters and restarters have been considered as smokers.

($p = 0.004$) and adjusted ($p = 0.06$) cumulative incidence was found among women than in men (Fig. 1). The adjusted cumulative incidence was highest in ages 30–50 and 70–80 years and lowest in ages 50–70 years (Fig. 2).

The annual incidence rate was estimated assuming the number of incident asthma cases to be constant. Thus the estimated crude incidence rate was 3.9 cases/1000/year and the adjusted incidence rate was 2.4 cases/1000/year.

Characteristics and risk factors of incident asthma

Of the 87 subjects with adjusted cumulative incident asthma, 68% reported attacks of SOB, 61% any wheeze, 32% recurrent wheeze, 72% use of asthma medication and 55% rhinitis. Non-smokers constituted 38% of the cases, 10% were smokers and 31% were ex-smokers. The majority were women (64%) and 56% were young adults aged 20–40 years in 1996. In a multivariate logistic regression analysis family history of asthma (OR 2.31, CI 95% 1.42–3.76), rhinitis (OR 2.25, CI 95% 1.43–3.53) and being an ex-smoker (OR 2.17, CI 95% 1.27–3.71) were all significant risk factors for adjusted incident asthma, while female sex did not reach statistical significance (Table 3).

Remission

In 1996, 295 subjects reported current asthma, i.e. physician-diagnosed asthma with symptoms or use of asthma

Table 1 Demographics in 1996 for responders and non-responders in 2006

Study population	Responders		Non-responders	
	Mean	Std	Mean	Std
Age	52	13	50	14
	<i>n</i>	%	<i>n</i>	%
Women	2474	55	625	49
Smokers	1342	30	464	37
Ex-smokers	900	20	237	19
Non-smokers	2169	49	551	44
Physician-diagnosed asthma	342	8	98	8
Longstanding cough	608	14	201	16

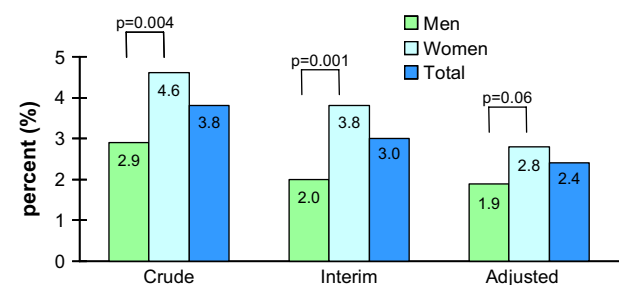


Figure 1 Cumulative incidence of physician-diagnosed asthma.

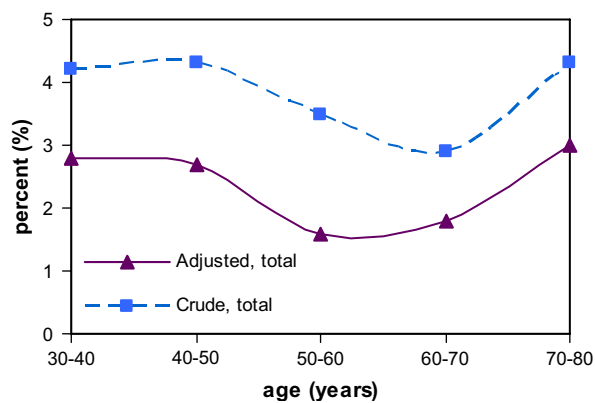


Figure 2 Crude and adjusted cumulative incidence of asthma by age group.

medication during the year preceding the survey in 1996. Using the above-mentioned definition, remission was found in 43 subjects. Hence, the 10-year remission was 14.6%. Remission was found in 12 men (11%) and 31 women (17%), $p = 0.16$. Subjects with remission had significantly less symptoms in 1996 and used asthma medication to a lesser degree (Fig. 3). Neither gender, age, a family history of asthma nor smoking habits had a significant effect on the probability of remission. Having rhinitis was inversely associated with remission (Table 3).

Relapse

In 1996, 47 subjects reported physician-diagnosed asthma but had not experienced asthma symptoms or use of asthma medication during the year prior to study entry. In 2006, 18 (38%) of these had relapse reporting at least one symptom, i.e. any wheeze (67%), recurrent wheeze (22%), attacks of

SOB (83%) or use of asthma medication (50%). Relapse was found in 7 men (29%) and 11 women (48%). None of the variables gender, age or smoking habits was associated with relapse assessed by a risk factor analysis. Subjects with a family history of asthma experienced relapse to a higher degree than subjects with no family history of asthma (OR 5.31, CI 95% 1.02–27.65).

Discussion

We report data on incidence, remission and relapse of adult asthma from a large population-based cohort with a high response rate. There is no evidence of a further increase in asthma incidence in Sweden when the present study, performed 1996–2006, and previous studies, performed 1986–1996 and 1990–2000, are viewed concurrently.^{5,7} The concept of asthma as a chronic disease was further verified with the findings of a low remission rate and a high relapse of physician-diagnosed asthma. A family history of asthma, rhinitis, being an ex-smoker and female sex was determinant of incident asthma.

Longitudinal studies of asthma are still sparse and have been focused on the incidence of asthma^{1–10} and only rarely on remission.^{11–15} Studies of relapse of asthma have been based on cohorts of children. The British 1958 birth cohort study^{21,22} and the Dunedin Multidisciplinary Health and Development study^{23,24} have followed cohorts of children to adult age. Studies of relapse in adult age are very scarce.¹¹

Studies of the incidence of asthma have been both retrospective⁹ and prospective^{1–7,10} and the reported incidence varies extensively. This variation is greatly influenced by several factors including the method used, the cohort's age composition, the definition of population at risk and the criteria of disease, which all vary across previous studies.^{5,25,26} Retrospective studies generally report lower incidence rates,^{9,25} and prospective studies

Table 3 Risk factors for crude incidence, adjusted incidence and remission of asthma

Independent variables		Dependent variables					
		Incidence of crude asthma		Incidence of adjusted asthma		Remission of asthma	
Variables	Categories	OR	95% CI	OR	95% CI	OR	95% CI
Age	30–40	1.00		1.00		1.00	
	41–50	1.04	0.67–1.63	0.98	0.55–1.76	0.62	0.24–1.61
	51–60	0.77	0.47–1.26	0.54	0.27–1.09	0.56	0.20–1.56
	61–70	0.8	0.46–1.38	0.67	0.33–1.39	0.82	0.30–2.26
	71–80	1.27	0.72–2.23	1.18	0.58–2.40	0.43	0.12–1.47
Gender	Men	1.00		1.00		1.00	
	Women	1.49	1.06–2.09	1.39	0.89–2.18	1.63	0.78–3.37
Family history	No	1.00		1.00		1.00	
	Yes	4.15	2.97–5.79	4.33	2.78–6.76	0.91	0.45–1.85
Rhinitis	No	1.00		1.00		1.00	
	Yes	2.74	1.97–3.81	2.21	1.41–3.48	0.33	0.16–0.67
Smoking	Non-smokers	1.00		1.00		1.00	
	Quitters	1.49	0.95–2.33	1.56	0.85–2.84	0.97	0.39–2.42
	Ex-smokers	1.58	1.03–2.42	2.05	1.20–3.52	1.51	0.63–3.65
	Smokers	1.02	0.63–1.66	0.84	0.40–1.73	0.53	0.16–1.69

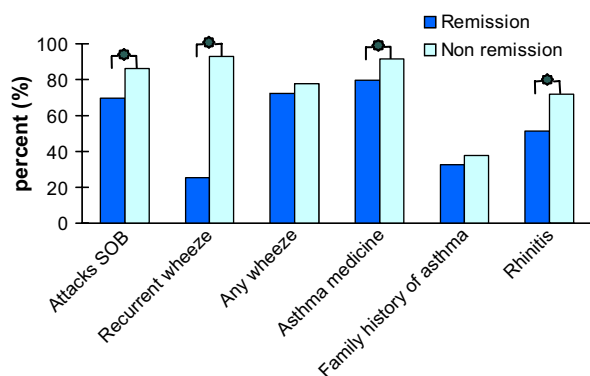


Figure 3 Symptoms in 1996 for subjects with and without remission in 2006.

with other definitions of population at risk report higher incidence rates since also non-diagnosed asthmatics at study start will be considered incident cases.

When comparing asthma incidence over time, or between geographical regions, using the same method is paramount for the results to be meaningful. Interestingly, the adjusted incidence rate of 2.4 cases/1000/year reported in this study running from 1996 to 2006 is similar to the incidence rate of 2.3/1000/year found in the OLIN studies from 1986 to 1996⁵ and RHINE studies from 1990 to 2000 that reported 2.1/1000/year⁷ (Fig. 4). These longitudinal studies over 10 years used the same method and similar definitions of population at risk, and we therefore conclude that the incidence of asthma among adults in Sweden has stabilized. Some other studies have shown that the prevalence of asthma is still increasing.^{6,17,27} The prevalence increase in respiratory symptoms and asthma in our cohort can be explained as an age-effect, as most symptoms increase by age. Whether or not asthma and symptoms are increasing in the society cannot be discussed based on our data. Our study was not a cross-sectional study, and thus it is not advisable to view the data as an actual increase in prevalence in the society, and hence these data are not shown. The increase in prevalence without increase in incidence has two main explanations. First, the incidence of asthma has increased in children and adolescents,^{28,29} and these subjects carry their

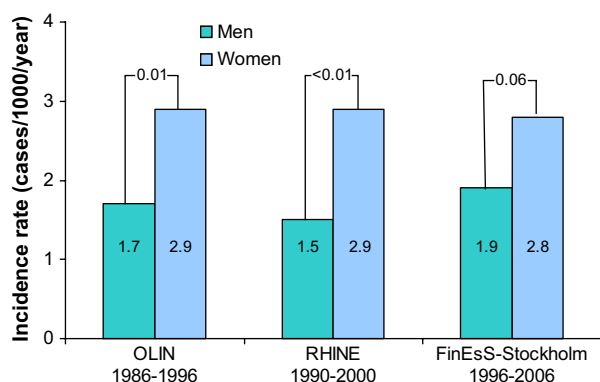


Figure 4 Adjusted incidence rates in recent Swedish longitudinal studies.

disease into adult age.^{23,30} Secondly, today, more patients with a milder disease are diagnosed with asthma than previously.⁵

A longitudinal study set-up is the only way to correctly calculate incidence and remission of asthma and it provides great advantages over cross-sectional studies when non-constant risk factors are assessed.⁴ If the studied disease has a low incidence, as asthma, large populations and/or long observation periods are necessary to identify determinants of disease.

Our finding that a family history of asthma was strongly associated with incident adult asthma is consistent with previous studies.^{4,9,31} Rhinitis was the second strongest risk factor for incident asthma. We believe rhinitis is a reasonable surrogate marker of allergic sensitization, which differentiates between allergic and non-allergic asthma. In analogy to children,³² different patterns of risk factors could be expected for allergic and non-allergic asthma. However, larger studies are needed to study this in population-based samples of adults. The incidence of physician-diagnosed asthma was higher among women compared to men as found in other studies.^{5,7,9,26}

The impact of smoking on asthma onset is controversial, as several studies report an increased risk^{5,9} which other prospective studies have failed to confirm.^{10,33,34} We found a significant association between ex-smoking and incident asthma, and a positive trend among those who quit smoking. This was not observed in smokers. One explanation may be that those who experience respiratory symptoms tend to stop smoking, while smokers with no respiratory symptoms continue smoking, the "healthy smoker effect".³⁵ These associations underline the importance of prospective population-based studies.

We found the remission over 10 years to be 14.6% and together with previous reports a homogenous picture with remission rates of about 1–2/100 asthmatics/year^{12–15} emerges. Studies of remission of asthma in children and adolescents report higher remission rates.^{11,24} Additional studies using the same definitions are essential to confirm the results. Remission of asthma was associated with mild disease prior to the first survey. The negative association between rhinitis and remission from asthma has been described previously.^{11–15}

The single available study of relapse among adult asthmatics with no symptoms or medications was conducted in 1972–1981¹¹ and reported a relapse rate of 38% over 9 years, similar to our study. Information on relapse has been investigated in child cohorts^{21–24} of which one has been followed-up at 42 years of age and relapse was rarer among adults than among children. In our 10-year study of an adult population, we have no information on childhood symptoms. This might underestimate the relapse rate since childhood symptoms are not remembered in up to 1/3 of adult subjects,²¹ and as a consequence also the true incidence rate could be somewhat lower than the found. Risk factor analysis was performed for relapse, but the subjects were too few to draw conclusions.

The validity of the current study must be considered high as it is a large longitudinal study with an excellent response rate. The responders at both surveys were highly representative of the original study population, supporting

a high internal validity. Moreover, the external validity must also be considered high with results comparable to several well-performed longitudinal studies.

In conclusion, this up-to-date longitudinal study with validated methods and a high participation rate vouch for solid and reliable results on the incidence, remission and relapse of adult asthma. In conjunction with previous studies no indication of an increased incidence of adult asthma could be seen. A low remission rate in combination with a high relapse rate strengthens the view of asthma as a chronic disease. The high relapse rate among subjects in remission might indicate that remission and relapse only are transitory variations in the clinical expression of asthma and further studies with a longer study period are needed to investigate the dynamics of this flux.

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Conflict of interest statement

Linda Ekerljung has no conflicts to disclose. Eva Rönmark has no conflicts to disclose. Kjell Larsson has received research grants from AstraZeneca, GlaxoSmithKline and Boehringer Ingelheim. He has also served in an advisory board and/or served as speaker and/or participated in education arranged by MSD, Pfizer and aforementioned companies. He has also grant monies from several research supporting foundations. Britt-Marie Sundblad has no conflicts to disclose. Anders Bjerg has no conflicts to disclose. Staffan Ahlstedt is employed by Phadia, otherwise no conflicts to disclose. Sven-Erik Dahlén has received grants from Aerocrine, AstraZeneca, Biolipox, Biovitrum, Centoror, GlaxoSmithKline and Merck & Co. He has served as a consultant and participated in speaking activities for several pharmaceutical companies. He has also grant monies from several research supporting foundations. Bo Lundbäck has received grants from GlaxoSmithKline, AstraZeneca and Boehringer Ingelheim. He has also served in an advisory board and/or served as speaker and/or participated in education arranged by GSK, AstraZeneca, Mondipharma and MSD.

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