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Remission of asthma: A prospective longitudinal study from Northern Europe (RHINE study)

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Short title: Asthma remission in Northern Europe

The aim was to study the remission rate of adult asthma in a general population sample in relation to age, sex, asthma symptoms, allergic rhinitis and smoking.

A follow-up of the random population samples from the European Community Respiratory Health Survey in Northern Europe was conducted between 1999 and 2001 on 1,153 individuals (26-53 yrs) with reported asthma. Remission was defined as no asthmatic symptoms in two consecutive years and no current use of asthma medication. Remission rates per 1000 person-years were calculated and Cox regression models, adjusting for confounders, were used for estimating Hazard Ratios (HR) with 95% confidence intervals (CI).

An average remission rate of 20.2/1000 person-years was found. There was no significant difference according to sex, in women the remission rate was 21.7/1000 person-years and in men it was 17.8/1000 person-years. An increased remission rate was observed among subjects quitting from smoking during the observation period. Subjects with no reporting of any asthma symptom at baseline had an increased remission rate. In the Cox regression model ex-smoking (HR 1.65, 95% CI 1.01-2.71) was associated with increased remission rate, and reporting of any asthma symptom at baseline was associated with decreased remission rate (HR 0.7, 95% CI 0.40 – 0.90).

In conclusion, this prospective longitudinal study quitting smoking and presence of mild disease appeared to favour remission.

Keywords: Age, allergic rhinitis, asthma, remission, sex, smoking

Introduction

There are very few publications on remission of asthma among adults. In most publications remission of asthma is defined as absence of asthma symptoms without current pharmacological therapy. An early study from Australia found that among children who reported wheezing at baseline 20% were in remission at the age of 21 (1), and 30% at 42 years of age (2). Several later studies showed similar results, for example, 20 to 25% of subjects with asthma went into remission over a period of 20 yrs (3-5). However, few of these studies are based on random population samples, which to some extent limit the external validity of the results.

Regarding predictors for remission of asthma there are even fewer studies. Rönmark et al followed 267 adults over 10 yrs and found that 6% went in remission (6). Those with mild asthma had an increased "risk" of remission. In another study on Swedish children, Rönmark et al found that a negative skin-prick test at baseline predicted remission of asthma (7). In the Swedish part of the European Community Respiratory Health Survey (ECRHS) low age appeared to predict remission (8). In a follow-up of a cohort of 613 children with wheezing at baseline showed that 25% were in remission at 26 yrs of age (9). Male sex, high age of asthma onset and normal lung function predicted remission.

There are no consistent definitions of asthma remission. In the Australian study remission was defined as being free from wheeze three years before follow-up investigation (1). Bronniman and Burrows defined remission as denying medications, asthma attacks or frequent attacks of shortness of breath with wheezing during the preceding year (3). Panhuysen et al defined "outgrown asthma" as no asthma symptoms, negative metacholine challenge test and normal FEV_1 at follow-up (5). Rönmark et al defined remission of asthma as no use of asthma medicines, no recurrent wheeze and no attacks of shortness of breath at follow-up (6). De Marco et al defined remission of asthma as not having an asthma attack during two years before follow-up and not use of asthma drugs in the last 12 months (10).

The present longitudinal study is a large follow-up of random population samples from the ERCHS in Northern Europe (Denmark, Estonia, Iceland, Norway and Sweden), termed RHINE (Respiratory Health in Northern Europe). The specific aim

was to study the remission rate in adult subjects with asthma, and to analyse the importance of certain predictors such as age, sex, allergic rhinitis, asthma symptoms and smoking.

Methods

The study population included 21,802 subjects born between 1945 and 1973 from Reykjavik in Iceland, Bergen in Norway, Umeå, Uppsala, and Göteborg in Sweden, Aarhus in Denmark, and Tartu in Estonia. These individuals participated in the baseline investigation which constituted stage 1 of the European Community Respiratory Health Survey (ECRHS I) (11). Participating centres performed the baseline investigation at different years, but all centres performed it during any year between 1989 to 1994. All subjects answered the ECRHS screening questionnaire featuring items about asthma symptoms the last 12 months such as wheezing, nocturnal chest tightness, nocturnal dyspnoea, nocturnal cough, asthma attacks, current use of asthma medication and allergic rhinitis.

At follow-up all subjects were mailed a questionnaire (12). The centres mailed the follow-up questionnaires at different years, but all centres performed the follow-up at any year during the period 1999 to 2001. Hence, the observation period is slightly different between the centres, in one centre it could be between 1989 and 1999 and in another centre it could be between 1994 and 2001. Altogether 16,191 (74.3 percent) answered the questionnaire. The first part of the questionnaire contained questions identical to the original version, i.e. items about asthma symptoms (12). A second part included items about self-reported asthma. Asthma was defined as a positive answer to either “Do you have or have you ever had asthma?” or “Have you ever had asthma diagnosed by a doctor?” (13). Year of onset of asthma was also requested (6, 14).

Thus, subjects in the present analysis included those who entered the observation period with asthma (based on positive answers in the questionnaire) and those who experienced asthma onset during the observation period. Using these criteria, 1,153 individuals entered the study who either had asthma at the first survey (1989-1994) or developed asthma during the observation period. These individuals represented the study population at risk (Table 1).

Remission of asthma was defined as an affirmative answer to the question “Which was the latest year you experienced asthma symptoms?” and no current use of asthma medication. Year of remission was obtained by adding two years to the year for the latest year of asthma symptoms. For example, if a subject reported onset of asthma in

1986 and reported the last occurrence of symptoms in 1990, then the year of remission was 1992.

Reporting at baseline of allergic rhinitis or any asthma symptoms (wheezing, nocturnal cough, nocturnal chest tightness, nocturnal dyspnoea or any asthma symptoms) during the last twelve months were analysed as predictors for the subsequent remission of asthma.

Smoking history at the end of follow-up was categorized as never smoker, former smoker, current smoker, or unknown. Never smoking person-years were defined from the start of follow-up until the end of the observation period if the person did not start to smoke during the follow-up period. In that case, smoking person-years were counted from start of smoking to cessation of smoking or until the end of the observation period. If the person smoked at the start of follow-up, smoking person-years were defined from the start of follow-up until the end of the observation period (or until cessation of smoking). Ex-smoking person-years were counted from the first year after cessation of smoking.

Statistical analyses

The statistical package SAS, version 8 was used for analyses. Remission rates were calculated as the number of remissions divided by the person-years at risk during the observation period. The subject ceased to contribute person-years when remission occurred. In some analyses the subjects were divided according to the median birth year, 1959.

P-values were calculated according to Mantel-Haenszel and p-values less than 0.05 were regarded as significant (15). Cox regression analyses (PROC PHREG) were performed with person-years under observation as the dependent variable and remission of asthma as an event, stratified for centre. Hazard ratios (HR) are given for explanatory variables included simultaneously in the model. In addition, there were separate models for women and men.

Results

A total number of 1,153 subjects entered the study which either had asthma at baseline investigation (performed between 1989 and 1994) or developed asthma during the observation period (between 1989 and 2001). Among these 1,153 individuals, representing a total of 10,608 person-years, 214 cases of asthma remission accumulated.

The remission rate was 20.2/1000 person-years. The univariate analyses of remission rates are shown in Table 2. The remission rate was decreased ($p<0.05$) among subjects reporting any asthma symptom the last 12 month at baseline compared to those not reporting any symptom. Subjects who quit smoking during follow-up had an increased remission rate ($p<0.05$). The remission rate among subjects with asthma onset before 20 yrs of age was 21.0/1000 person-years as compared to 19.4/1000 person-years among those with asthma onset after 20 yrs of age.

Compared to the Swedish centres (23.6/1000, n=118) the remission rate was quite similar in Bergen, Norway (15.0/1000, n=30), Reykjavik, Iceland (21.0/1000, n=33 and Aarhus, Denmark (18.0/1000, n=22). However in Tartu, Estonia the remission rate was significantly ($p<0.05$) higher (61.1/1000, n=11) compared to the Swedish centres.

The results from Cox regression models are shown in Table 3. When all predictors were kept in the same model, there was a decreased remission rate among subjects reporting any asthma symptom the last 12 months at baseline (HR 0.7, 95% CI 0.49-0.90). Among ex-smokers there was an increased remission rate among women (HR 1.9, 95% CI 1.03-3.65), but not among men. If year of asthma onset was introduced in the models, the results were similar.

Discussion

In the present prospective longitudinal study, remission rate of asthma was found to be 20.2/1000 person-years during the period 1989 to 2001. In other words, approximately 20% of subjects recovered from their asthma during a ten year period. A main finding was that subjects with asthma that reported asthma symptoms at baseline, were less likely to recover from their asthma (i.e subjects with a less severe asthma had an increased remission rate).

There are few studies on remission of asthma among adults. Several quite different definitions of remission have been used, which may partly explain the varying results between studies. In the present study we defined remission as no current use of asthma medication and no asthmatic symptoms during the last two years.

One of the few studies on asthma remission rate in adults investigated a cohort of 300 middle-aged and elderly subjects (7). This study reported remission (no use of asthma medicines, no recurrent wheezing, and no attack of shortness of breath) in 6% of subjects at a follow-up 10 yrs after a validated diagnosis of current asthma, equivalent to a remission rate of 6/1000 person-years. In 60 subjects with suspected asthma 22% were in remission at the 10-yr follow-up. The study concluded that remission was associated with mild disease.

We found in the present study that subjects reporting symptoms at baseline had decreased probability of remission during the follow-up. An obvious explanation is that subjects with mild disease have an increased probability of remission. Similar observations have also been published by other groups (3, 5-6).

We did not find any relation between remission and either birth-year or age of asthma-onset. Our study focuses on asthma remission in a population of adults born 1945-1973. Most studies published indicate that remission is most common in younger individuals (2, 5, 16, 17). One study found that the remission rate was highest in subjects below 30 yrs at entry and lowest in those aged 30 to 59 yrs. However, after the age of 60 the remission rate increased (3). In an Italian study remission was strongly influenced by the age at onset of asthma, with a stepwise decreasing probability of remission from 0 to 44 years of age (10). Moreover, they found that

remission appears to occur principally during the first years after the onset of the disease. In our study, there was a tendency for subjects born after 1959 to have a higher remission rate than subjects born 1945-1959, thus in line with previous studies. We did not observe any difference with regard to age of asthma onset, as the remission rate among subjects with asthma onset before 20 yrs was similar to those with asthma onset after 20 yrs of age.

The relationship between smoking and asthma is complex. However, in our analysis quitting smoking was found to favour remission of asthma. This finding is supported by Rönmark et al who concluded that remission of asthma is associated with cessation of smoking (7).

The present study has two key strengths: (1) its size and (2) its well-defined population. Out of 1,153 asthmatic individuals, 214 were considered to be in a state of remission, resulting in one of the largest studies ever examining asthma remission and its predictors. As discussed in a previous paper, a weakness of the study is that diagnostic traditions appear to differ between countries (12). However, this was not reflected in the remission rate in Iceland, which was similar to that of other countries, despite less severe cases receiving a physician´s diagnosis of asthma. In Estonia, we have previously observed that individuals diagnosed with asthma may have a severe disease (12). Nonetheless, Estonia had a high remission rate in this study. We have no explanation to this unexpected observation.

A weakness of the study is that it is based on self-reported data. Self-reported physician-diagnosed asthma is biased towards severity, i.e. subjects with mild asthma are more prone to deny asthma (18). Hence, our estimations of remission rate are probably underestimating the true remission rate, as subjects with mild disease are underrepresented among the asthmatics.

In conclusion, our main observation is that smoking cessation favoured remission. This further strengthens the importance of implementing smoking cessation programs among subjects with asthma.

Table 1. Birth year, sex, asthma symptoms at baseline and smoking habits at follow-up in a longitudinal study between 1989 to 2001 of 1,153 adult subjects with asthma from Northern Europe.

Predictor	**All subjects (n = 1,153)**
Subjects born after 1959	50.8% (n=586)
Subjects born 1945-1959	49.2% (n=567)
Women	60.1% (n = 693)
Men	39.9% (n=460)
Never smokers (at follow-up)	44.0% (n = 507)
Former smokers (at follow-up)	26.4% (n = 305)
Current smokers (at follow-up)	28.0% (n = 323)
Unknown smoking habits	1.6% (n = 18)
Allergic rhinitis (at baseline)	52.6% (n = 606)
Wheezing the last 12 months(at baseline)	63.3% (n =730)
Nocturnal cough the last 12 months(at baseline)	41.7% (n = 481)
Nocturnal chest tightness the last 12 months (at baseline)	33.1% (n=382)
Nocturnal dyspnoea the last 12 months (at baseline)	22.3% (n=257)
Any attacks of asthma the last 12 months (at baseline)	30.7% (n=349)
Any asthma symptom the last 12 months (at baseline)[1]	78.3 ((n=903)

1. Wheezing, asthma attacks or nocturnal cough, chest tightness, or dyspnoea the last 12 months

Table 2

Number of remission cases of asthma among 1,153 adult asthmatic subjects from Northern Europe and remission rates (cases/1000 person-years under observation), in relation to sex, birth year, smoking and asthma symptoms at baseline.

Predictor	N	Remission rate
Females	38	21.7
Males	76	17.8
Subjects born 1960-1973	119	22.5
Subjects born 1945-1959	95	17.9
Smokers	56	19.0
Quitters[1]	24	36.9[2]
Never-smokers	101	21.7
Any asthma symptom the last 12 months (at baseline)		
Yes	903	18.4
No	250	26.5[3]

1. These are subjects quit smoking during the observation period. Subjects quit smoking before the first survey is not included.
2. $p<0.05$ compared to never-smokers.
3. $p<0.05$ (Yes vs No)

Table 3. Hazard ratios (HR) for remission of asthma during the period between 1989 and 2001 in relation to sex, smoking, asthma symptoms, and allergic rhinitis at start of follow-up. Smoking is analyzed as a time dependent variable. Results based on a Cox regression model adjusted for centre and birth-year.

Predictor	**Hazard ratio (95% confidence interval)**		
	All	**Females**	**Males**
Females	1.2 (0.90-1.59)	N.a.	N.a.
Smoking	1.0 (0.72-1.30)	1.1 (0.74-1.53)	0.8 (0.46-1.30)
Ex-smoking	1.6 (0.99-2.68)	1.9 (1.03-3.65)	1.2 (0.52-2.61)
Allergic rhinitis (at baseline)	0.9 (0.69-1.19)	1.3 (0.89-1.80)	0.9 (0.54-1.28)
Any asthma symptom the last 12 monts (at baseline)	0.7 (0.49-0.90)	0.8 (0.55-1.22)	0.5 (0.31-0.82)

References

1. Martin AJ, Landau LI, Phelan PD. The natural history of asthma to adult life. Brit Med J 1980;280:1397-1400.

2. Phelan PD, Robertson CF, Olionsky A. The Melbourne asthma study: 1964 – 1999. J Allergy Clin Immunol 2002;109:1397-1400 .

3. Bronnimann S, Burrows B. A prospective study of the natural history of asthma. Remission and relapse rates. Chest 1986;90:480-4.

4. Roorda RJ, Gerritsen J, van Aalderen VM, Schoutjen JP, Veltman JC, Weiss ST, Knol K. Risk factors for the persistence of respiratory symptoms in childhood asthma. Am Rev Respir Dis 1993;148 (pt 1):1490-1495.

5. Panhuysen CI, Vonk JM, Koeter GH, Schouten JP, van Altena R, Bleecker ER, Postma DS. Adult patients may outgrow their asthma: a 25-year follow-up study. Am J Respir Crit Care Med. 1997;155:1267-72. Erratum in: Am J Respir Crit Care Med 1997;156(2 Pt 1):674.

6. Rönmark E, Jönsson E, Lundbäck B. Remission of asthma in the middle aged and elderly: Report from the Obstructive Lung Disease in Northern Sweden study. Thorax 1999;54:611-613.

7. Rönmark E, Jönsson E, Platts-Mills T, Lundbäck B. Incidence and remission of asthma in schoolchildren: Report from the Obstructive Lung Disease in Northern Sweden Studies. Pediatrics 2001;107:e37

8. Plaschke PP, Janson C, Norrman E, Björnsson E, Ellbjär S, Järvholm B. Onset and remission of allergic rhinitis and asthma and the relationship with atopic sensitization and smoking. Am J Respir Crit Care Med 2000;162:920-4.

9. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor R, Flannery EM, Cowan JO, Herbison GP, Silva PA, Poulton R. A longitudinal, population-based cohort study of childhood asthma followed to adulthood. N Engl J Med 2003;349:1414-1422.

10. De Marco R, Locatelli F, Cerveri I, Bugiani M, Marinoni A, Giammanco G. Incidence and remission of asthma: a retrospective study on the natural history of asthma in Italy. J Allergy Clin Immunol 2002:110:228-235.
11. Janson C, Anto J, Burney P, Chinn S, de Marco R, Heinrich J, Jarvis D, Kuenzli N, Leynaert B, Luczynska C, Neukirch F, Svanes C, Sunyer J, Wjst M. The European Community Respiratory Health Survey: what are the main results so far? Eur Respir J 2001:18:598-611.

12. Toren K, Gislason T, Omenaas E, Jögi R, Forsberg B, Nystrom L, Olin AC, Svanes C, Janson C; RHINE Group. A prospective study of asthma incidence and its predictors: the RHINE study. Eur Respir J 2004:24:942-946.

13. Toren K, Brisman J, Järvholm B. Asthma and asthma-like symptoms in adults assessed by questionnaires. Chest. 1993:104:600-608.

14. Andersson E, Knutsson A, Hagberg S, Nilsson T, Karlsson B, Alfredsson L, Torén K. Incidence of asthma among workers exposed to sulphur dioxide and other irritant gases. Eur Respir J 2006;27:720-725.

15. Altman DG. Practical statistics for medical research. Chapman&Hall, London, 1991.

16. Kelly WJ, Hudson I, Phelan PD, Pain MC, Olinsky A. Childhood asthma in adult life: a further study at 28 years of age. Br Med J 1987:294:1059-1062.

17. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. Brit Med J 1996:312:1195-1199.

18. Torén K, Palmqvist M, Löwhagen O, Balder B, Tunsäter A. Accuracy of self-reported year of asthma-onset. J Clin Epidemiol 2006;59:90-93.