



# Remission of asthma: a prospective longitudinal study from northern Europe (RHINE study)

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**ABSTRACT:** The aim of the present study was to investigate 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 from 1999–2001 on 1,153 individuals (aged 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 1,000 person-yrs were calculated and Cox regression models, adjusting for confounders, were used to estimate hazard ratios (HR) with 95% confidence intervals (CI).

An average remission rate of 20.2 per 1,000 person-yrs was found. There was no significant difference according to sex; the remission rates were 21.7 and 17.8 per 1,000 person-yrs in females and males, respectively. An increased remission rate was observed among subjects who quit smoking during the observation period. Subjects not reporting 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 any asthma symptom at baseline was associated with decreased remission rate (HR 0.7, 95% CI 0.40–0.90).

In conclusion, the present prospective longitudinal study showed that quitting smoking and the presence of mild disease appeared to favour remission.

**KEYWORDS:** Age, allergic rhinitis, asthma, remission, sex, smoking

There are very few publications concerning the 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 yrs [1] and 30% at 42 yrs of age [2]. Several later studies showed similar results, e.g. 20–25% 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.* [6] followed 267 adults over 10 yrs and found that 6% went into remission. Those with mild asthma

had an increased “risk” of remission. In another study of Swedish children, RÖNMARK *et al.* [7] found that a negative skin-prick test at baseline predicted remission of asthma. In the Swedish part of the European Community Respiratory Health Survey (ECRHS), young age appeared to predict remission [8]. Follow-up of a cohort of 613 children with wheezing at baseline showed that 25% were in remission at 26 yrs of age [9]. The male sex, high age of asthma onset and normal lung function were predictors of remission.

There are no consistent definitions of asthma remission. In the Australian study, remission was defined as being free from wheeze 3 yrs before follow-up investigation [1]. BRONNIMANN and BURROWS [3] defined remission as no medication, asthma attacks nor frequent attacks of shortness of breath with wheezing during the preceding year. PANHUYSEN *et al.* [5] defined “outgrown

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asthma" as no asthma symptoms, negative metacholine challenge test and normal forced expiratory volume in one second at follow-up. RÖNMARK *et al.* [6] defined remission of asthma as no use of asthma medicines, no recurrent wheeze and no attacks of shortness of breath at follow-up. DE MARCO *et al.* [10] defined remission of asthma as not having an asthma attack during the 2 yrs before follow-up and no use of asthma drugs in the last 12 months.

The present longitudinal study is a large follow-up of random population samples from the ECRHS in Northern Europe (*i.e.* 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 1945–1973 from Reykjavik (Iceland), Bergen (Norway), Umeå, Uppsala and Göteborg (Sweden), Aarhus (Denmark) and Tartu (Estonia). These individuals participated in the baseline investigation which constituted stage 1 of the ECRHS, *i.e.* ECRHS I [11]. Participating centres performed the baseline investigation at different years, but all centres performed it during any year between 1989–1994. All subjects answered the ECRHS screening questionnaire featuring items about asthma symptoms in the previous 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 in different years, but all centres performed the follow-up at any year during the period 1999–2001. Hence, the observation period is slightly different between the centres, in one centre it could be 1989–1999 and in another centre it could be 1994–2001. Altogether 16,191 (74.3%) subjects 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]. The 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 a positive 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 2 yrs to 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.

**TABLE 1** Study population at follow-up in a longitudinal study between 1989–2001 of adult subjects with asthma from northern Europe

Predictor	
<b>Total subjects</b>	1153
<b>Subjects born after 1959</b>	586 (50.8)
<b>Subjects born 1945–1959</b>	567 (49.2)
<b>Female</b>	693 (60.1)
<b>Male</b>	460 (39.9)
<b>Never-smokers at follow-up</b>	507 (44.0)
<b>Former smokers at follow-up</b>	305 (26.4)
<b>Current smokers at follow-up</b>	323 (28.0)
<b>Unknown smoking habits</b>	18 (1.6)
<b>Allergic rhinitis at baseline</b>	606 (52.6)
<b>Wheezing in the last 12 months at baseline</b>	730 (63.3)
<b>Nocturnal cough in the last 12 months at baseline</b>	481 (41.7)
<b>Nocturnal chest tightness in the last 12 months at baseline</b>	382 (33.1)
<b>Nocturnal dyspnoea in the last 12 months at baseline</b>	257 (22.3)
<b>Any attacks of asthma in the last 12 months at baseline</b>	349 (30.7)
<b>Any asthma symptom in the last 12 months at baseline<sup>#</sup></b>	903 (78.3)

Data are presented as n or n (%). <sup>#</sup>: wheezing, asthma attacks or nocturnal cough, chest tightness or dyspnoea in the last 12 months.

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 12 months were analysed as predictors for the subsequent remission of asthma.

Smoking history at the end of follow-up was categorised as never-smoker, former smoker, current smoker or unknown. Never-smoking person-yrs 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 which case, smoking person-yrs 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-yrs were defined from the start of follow-up until the end of the observation period (or until cessation of smoking). Ex-smoking person-yrs were counted from the first year after cessation of smoking.

## Statistical analyses

Remission rates were calculated as the number of remissions divided by the person-yrs at risk during the observation period. The subject ceased to contribute person-yrs when remission occurred. In some analyses the subjects were divided according to the median birth year, which was 1959.

The Mantel-Haenszel method was used for the calculation of p-values. A p-value of 0.05 was regarded as significant [15]. Cox regression analyses (PROC PHREG) were performed with person-yrs 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 females and males.

**RESULTS**

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

The remission rate was 20.2 per 1,000 person-yrs. 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 in the last 12 months at baseline compared with 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 per 1,000 person-yrs compared with 19.4 per 1,000 person-yrs among those with asthma onset after 20 yrs of age.

Compared with the Swedish centres (23.6 per 1,000 person-yrs;  $n = 118$ ) the remission rate was quite similar in Bergen (15.0 per 1,000 person-yrs;  $n = 30$ ), Reykjavik (21.0 per 1,000 person-yrs;  $n = 33$ ) and Aarhus (18.0 per 1,000 person-yrs;  $n = 22$ ). However, in Tartu the remission rate was significantly ( $p < 0.05$ ) higher (61.1 per 1,000 person-yrs;  $n = 11$ ) compared with 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 in the last 12 months at baseline (HR 0.7, 95%

**TABLE 3** Hazard ratios (HR) for remission of asthma during the period 1989–2001 in relation to sex, smoking, asthma symptoms and allergic rhinitis at start of follow-up

Predictor	HR (95% CI)		
	All	Females	Males
<b>Females</b>	1.2 (0.90–1.59)	NA	NA
<b>Smoking</b>	1.0 (0.72–1.30)	1.1 (0.74–1.53)	0.8 (0.46–1.30)
<b>Ex-smokers</b>	1.6 (0.99–2.68)	1.9 (1.03–3.65)	1.2 (0.52–2.61)
<b>Allergic rhinitis at baseline</b>	0.9 (0.69–1.19)	1.3 (0.89–1.80)	0.9 (0.54–1.28)
<b>Any asthma symptom in the last 12 months at baseline</b>	0.7 (0.49–0.90)	0.8 (0.55–1.22)	0.5 (0.31–0.82)

Smoking is analysed as a time dependent variable. Results are based on a Cox regression model adjusted for centre and birth year. CI: confidence interval; NA: not available.

confidence interval (CI) 0.49–0.90). Among ex-smokers there was an increased remission rate among females (HR 1.9, 95% CI 1.03–3.65), but not among males. If year of asthma onset was introduced to the models, the results were similar.

**DISCUSSION**

In the present prospective longitudinal study, the remission rate of asthma was found to be 20.2 per 1,000 person-yrs during the period 1989–2001, *i.e.* ~20% of subjects recovered from their asthma during a 10-yr period. A main finding was that subjects with asthma who 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, remission was defined as no current use of asthma medication and no asthmatic symptoms during the last 2 yrs.

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 attacks 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 six per 1,000 person-yrs. 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.

The present study found 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].

**TABLE 2** Number of remission cases of asthma among 1,153 adult asthmatic subjects from Northern Europe and remission rates in relation to sex, birth year, smoking and asthma symptoms at baseline

Predictor	n	Remission rate
<b>Females</b>	38	21.7
<b>Males</b>	76	17.8
<b>Subjects born 1960–1973</b>	119	22.5
<b>Subjects born 1945–1959</b>	95	17.9
<b>Smokers</b>	56	19.0
<b>Quitters<sup>#</sup></b>	24	36.9*
<b>Never-smokers</b>	101	21.7
<b>Any asthma symptom in the last 12 months at baseline</b>		
Yes	903	18.4
No	250	26.5 <sup>†</sup>

Remission rate is presented as cases per 1,000 person-yrs under observation. <sup>#</sup>: these are subjects who quit smoking during the observation period. Subjects who quit smoking before the first survey are not included; <sup>†</sup>:  $p < 0.05$  yes versus no. \*:  $p < 0.05$  compared with never-smokers.

The current authors did not find any relationship between remission and either birth year or age of asthma onset. The present study focused on asthma remission in a population of adults born between 1945–1973. Most published studies indicate that remission is most common in younger individuals [2, 5, 16, 17]. One study found that the remission rate was highest in subjects aged <30 yrs at entry and lowest in those aged 30–59 yrs. However, in subjects aged >60 yrs 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 0–44 yrs of age [10]. Moreover, it was found that remission appears to occur principally during the first years after the onset of the disease. In the present study, there was a tendency for subjects born after 1959 to have a higher remission rate than subjects born between 1945–1959; this is in agreement with previous studies. The current authors 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 the present analysis quitting smoking was found to favour remission of asthma. This finding is supported by RÖNMARK *et al.* [7], who concluded that remission of asthma is associated with cessation of smoking.

The present study has two key strengths: its size and 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 ever studies 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, it has been previously observed that individuals diagnosed with asthma may have a severe disease [12]. Nonetheless, Estonia had a high remission rate in the present study. The current authors have no explanation for 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, the estimations of remission rate are probably underestimating the true remission rate, as subjects with mild disease are underrepresented among asthmatics.

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

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