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Title:

Clinical predictors of remission and persistence of adult-onset asthma

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ABSTRACT

BACKGROUND: Adult-onset asthma is an important but relatively understudied asthma phenotype and little is known about its natural course and prognosis. The remission rate is believed to be low, and it is still obscure which factors predict remission or persistence of the disease.

OBJECTIVE: To determine the remission rate, and identify predictors of persistence and remission of adult-onset asthma.

METHODS: Two hundred adult patients with recently diagnosed (<1 year) asthma were recruited from secondary and tertiary pulmonary clinics and prospectively followed for 5 years. Clinical, functional and inflammatory parameters were assessed at baseline and at yearly visits. Asthma remission was defined as absence of asthma symptoms for ≥ 1 year and no asthma medication use for ≥ 1 year. Descriptive statistics and logistic regression analysis were performed.

RESULTS: Five-year follow-up data of 170 patients (85%) was available. Of these, 27 patients (15.9%) experienced asthma remission. Patients with asthma persistence were older, had worse asthma control, required higher doses of inhaled corticosteroids, had more severe airway hyperresponsiveness, more often nasal polyps and higher levels of blood neutrophils as compared to patients who experienced clinical remission.

In a multivariable logistic regression analysis, only moderate-severe bronchial hyperresponsiveness and nasal polyps were independent predictors of asthma persistence. Patients with these two characteristics had less than 1% chance of asthma remission.

CONCLUSION: One in six patients with adult-onset asthma experiences remission within the first 5 years of the disease. In patients with moderate to severe bronchial hyperresponsiveness and nasal polyposis the chance of remission is close to zero.

Clinical implications

Nasal polyps and airway hyperresponsiveness are clinical indicators to identify adult-onset asthma patients at risk of persistent asthma; closer monitoring and follow-up of patients with these characteristics might improve asthma outcomes.

Capsule summary

Adult-onset asthma remission occurs in 16% of the patients within 5 years after diagnosis. Nasal polyposis and moderate to severe bronchial hyperresponsiveness at the time of asthma diagnosis reduces the chance of remission to <1%.

Key words

Asthma; adult-onset; remission; persistence; prognosis; clinical predictors; prospective study.

Abbreviations

ACQ (asthma control questionnaire), AQLQ (asthma quality of life questionnaire), BMI (body mass index), ICS (inhaled corticosteroids), FEV₁ (forced expiratory volume in 1 second), FeNO (fraction of exhaled nitric oxide), FVC (forced vital capacity), GERD (gastroesophageal reflux disease), GINA (global initiative of asthma), PC20 (provocative concentration of methacholine causing a 20% fall in FEV₁), RV (residual volume), TLC (total lung capacity), DLCOc/VA (diffusing capacity of the lung for carbon monoxide divided by alveolar volume)

INTRODUCTION

Adult-onset asthma is a clinically important, but relatively understudied phenotype of asthma.¹ In contrast to childhood atopic asthma, adult-onset asthma had not been investigated systematically until 2004.² Most available data about adult-onset asthma come from cross-sectional studies and have shown that it is a heterogeneous condition with at least three distinct phenotypes.³ Adult-onset asthma is suggested to be more severe than childhood onset asthma, less responsive to treatment and associated with accelerated decline in lung function.⁴ Remission of childhood-onset asthma occurs in up to two-thirds of the patients,⁵⁻⁷ whereas adult-onset asthma has been reported to be more chronic with a much lower remission rate.^{6, 8-13} However, most of these studies are difficult to interpret because they are based on "self-reported asthma" or "self-reported physician-diagnosed asthma" or database data in which a mixed childhood- and adult-onset population is studied. Only two studies prospectively followed patients with adult-onset asthma, but unfortunately these studies lacked power to test predictors of remission by multivariable analysis.^{9, 13} Knowledge about the clinical course and outcome of adult-onset asthma and its determinants may be important for several reasons. For patients, it is important to know the chance of disease remission or persistence so that they can adjust plans for their future life. For physicians, knowing risk factors of asthma persistence might serve to identify treatable factors with a potential beneficial effect on the course of the disease.¹⁴ For researchers, identification of determinants of asthma outcome might help to better understand the aetiology of the disease. Finally, for policy makers and health care payers, knowledge of asthma remission and persistence rates will allow more accurate estimates of healthcare expenditure.

The aim of the present study was to identify clinical, functional or inflammatory predictors of asthma persistence and remission in a prospectively followed cohort of adults with newly diagnosed, well-defined asthma.

METHODS

Patients

Two hundred adults with new-onset asthma were recruited from one academic and two non-academic pulmonary outpatient clinics between 2009 and 2011 and were prospectively followed for 5 years. All patients had a doctor's diagnosis of new-onset asthma and documented evidence of reversibility in $FEV_1 \geq 12\%$ or airway hyperresponsiveness.¹⁵ Patients were excluded if they had a history of asthma or chronic airways disease in childhood. Detailed inclusion and exclusion criteria are described in the online repository. The study was approved by the AMC Medical Ethics Board and registered in the Dutch trial register (NTR1846). All participants were informed and gave written informed consent.

Study design

This prospective longitudinal cohort study was part of the ADONIS-study (Adult-onset asthma and inflammatory subphenotypes).¹⁶ At baseline, patients underwent a comprehensive assessment of clinical, functional and inflammatory parameters (Figure 1). Thereafter, they were treated in regular healthcare facilities. Patients were contacted and invited for a limited reassessment at yearly intervals. Between 4 to 5 years post diagnosis an extensive reassessment of baseline measurements was done. If patients could not be reached by phone, email or postal mail, basic information about asthma symptoms and medication was collected via their general practitioner.

Study measurements

Clinical measurements – A comprehensive history was taken, including questions about asthma symptoms, medication use and healthcare utilization in the past year. Patients completed questionnaires including the asthma control questionnaire (ACQ-6; uncontrolled asthma defined as ACQ-score ≥ 1.5),¹⁷ asthma quality of life questionnaire (AQLQ), and the Sino-nasal Outcome Test (SNOT-22).¹⁸ Obesity was defined as a BMI $\geq 30 \text{ kg/m}^2$.

Lung function measurements – Pre- and post-bronchodilator spirometry (FEV₁ and forced vital capacity (FVC)) was performed according to international standards.¹⁹ Diffusion capacity of the lungs for carbon monoxide divided by alveolar volume (DLCOc/VA) was measured with single breath measurement.²⁰ Total lung capacity (TLC) and residual volume (RV) were measured by body plethysmography. Bronchial challenge test was performed with inhaled methacholine to establish the concentration causing a 20% fall in FEV₁ (PC₂₀-methacholine). In case patients did not reach a $\geq 20\%$ fall in FEV₁, a level of 32 mg/ml methacholine was taken as default value. Bronchial hyperresponsiveness can be divided into: mild 1-4mg/ml, moderate to severe <1.0 mg/ml.²¹

Inflammatory parameters - Fraction of exhaled nitric oxide (FeNO) was measured at a flow rate of 50mL/s (NIOX System, Aerocrine, Sweden).²² Venous blood was collected and differential white blood cell count was performed. Total and specific IgE to common aeroallergens were measured by ImmunoCAP; atopy was defined as IgE >0.35 Ku/L for at least one allergen. Sputum induction was performed according to international standards.²³ Sputum processing was done according to full sample method and differential cell counts were stained and analyzed on cytopsin preparations.

Sinonasal imaging - The presence of nasal polyps was evaluated based on sinus CT-scanning and nasal endoscopy.²⁴

Assessment of asthma remission and persistence

Clinical asthma remission^{8-10, 25} was the primary outcome of the study and defined as: no asthma symptoms for ≥ 1 year and no asthma medication use for ≥ 1 year at the 5-year follow-up visit. Asthma persistence was defined as presence of asthma symptoms in the last year or use of any asthma medication (beta-2-agonists or inhaled corticosteroids) in the last year.

Secondary outcomes included pathophysiological confirmation of clinical remission by means of change in lung function, bronchial hyperresponsiveness and inflammatory markers.⁹

Statistical analysis

Comparisons of baseline variables between patients in remission and patients with persistent asthma were done by Student t-test, Mann Withney-U test or chi-square. Wilcoxon signed rank test and paired t-tests were used to analyze the changes of variables over time.

Univariate logistic regression was used to select significant baseline variables for the multivariable logistic regression model. The significant predictor variables were used in a multivariable binary logistic regression model and selected by backward selection of the model. Results are expressed as beta with standard error (SE). Statistical significance was set at a P value of less than .05.

Analyses were performed in SPSS version 23.0 (IBM SPSS, Chicago, Ill) and R-studio V0.99.467, Package logistf (Integrated development environment for R, Boston, MA).

RESULTS

Clinical data of 170 patients (85% of initial cohort, see Figure 1) were available at 5-year follow-up (mean follow-up duration 4.8 ± 0.6 years); of which 108 (64%) patients underwent an evaluation in the lung function laboratory, 27 (16%) patients were contacted by telephone, and from 35 (21%) patients data were obtained from the primary care database. Additional data collected at yearly intervals were obtained from 75% of the patients. Patients who were lost to follow-up differed slightly from the rest of the cohort with respect to a younger age and lower incidence of nasal polyposis, there was no difference in smoking status (data not shown).

Incidence and characteristics of patients with asthma remission or persistence

Clinical remission of asthma occurred in 27 out of 170 patients (15.9%). Remission was observed in the course of time, the median duration from baseline to remission was 45 months (range 9-45 months).

At baseline, patients with persistent asthma were older, had worse asthma control (asthma control questionnaire (ACQ)-score 1.34 vs 0.89, $p=0.026$), required higher doses of inhaled corticosteroids (median fluticasone equivalent 313 μg vs 250 μg , $p=0.007$), had more severe bronchial hyperresponsiveness (PC_{20} -methacholine 2.7 vs 5.8 mg/ml, $p=0.003$), were more often diagnosed with nasal polyps (25% vs 0%, $p=0.004$) and had higher levels of blood neutrophils as compared to patients who experienced clinical remission after 5 years. There was no difference between the two groups in lung function, percentage of eosinophils in blood or sputum, or level of exhaled nitric oxide (Table I).

At 5-year follow-up, patients in remission showed a significant reduction in ICS dose and ACQ-score. These patients also showed a reduction in PC_{20} -methacholine over time, resulting in the absence of bronchial hyperresponsiveness in the majority of patients. Patients with asthma persistence did not show a significant change in PC_{20} -methacholine, but showed an increase in persistent airway obstruction as reflected by a lower post-bronchodilator FEV_1/FVC . Neither group showed significant changes in markers of

eosinophilic inflammation, however patients with persistent asthma showed an increase in sputum neutrophils (Table II). In a post hoc analysis, patients with asthma persistence with and without nasal polyps were examined in more detail (Table E I). Furthermore, the observed increase of sputum neutrophil levels in patients with asthma persistence appeared to be only present in patients without nasal polyps ($p=0.004$, $n=30$) and not in those with nasal polyps ($p=0.122$, $n=15$).

Predictors of asthma remission and persistence

Univariate logistic regression analysis showed that age, ICS-dose, ACQ-score, PC_{20} -methacholine and nasal polyps were significant predictors of asthma outcome. Multivariable logistic regression showed that more severe bronchial hyperresponsiveness (lower PC_{20} -methacholine, per step decrease in dose: $\text{Beta(SE)}=0.99(0.39)$, $p=0.005$) and the presence of nasal polyps ($\text{Beta(SE)}=2.96(1.47)$, $p=0.001$) were independent predictors of asthma persistence. The probability of asthma remission can be calculated by the following formula: $x/(1+x)$, where $x = e^{(-4.75791 + (\text{nasal polyps} \times 2.9419) + ((\text{Log10}(PC_{20}\text{-Metacholine})) \times 0.93938))}$. Thus, when applying this model to an imaginary patient with nasal polyps and PC_{20} -methacholine of 1 mg/ml at the time of asthma diagnosis this would give a chance of less than 1% for asthma remission within the next 5 years (Figure 2).

DISCUSSION

This study shows that one in six patients with adult-onset asthma experiences clinical remission within the first 5 years of the disease, which is more than previously reported. Independent risk factors of asthma persistence include moderate to severe bronchial hyperresponsiveness and nasal polyposis, which together reduce the chance of asthma remission to less than 1%. These results demonstrate that asthma severity - defined by BHR - and upper airways involvement at the time of asthma diagnosis are major outcome determinants of newly diagnosed asthma in adults.

In the present study we found an asthma remission rate of 3.2% per year, which is relatively high. In the literature, a wide range of remission rates in adults with asthma has been reported varying from 0.6 to 3% per year.^{6, 8, 10, 25, 26} An important problem when comparing these figures with those from our study is the lack of a common definition of asthma remission. Furthermore, most studies have not differentiated between childhood and adult-onset asthma, which most likely caused an overestimation of the remission rate. Few studies specifically addressed remission rates in adult-onset asthma and only one study exclusively included patients with new-onset adult asthma.⁹ The latter study found a clinical remission rate of 0.8% per year, which is considerably lower than in our study. Even after applying more strict rules for remission, by including normal lung function and absence of airway hyperresponsiveness, the remission rate was still higher than previously reported (Figure E1).⁹ This discrepancy might be due to differences in asthma severity of the patients, although this is not likely. All our patients were recruited from secondary or tertiary care centres, and diagnosed with asthma by pulmonologists, which was confirmed by spirometry or airway hyperresponsiveness tests. One retrospective study suggested that remission rates were relatively high early after disease onset, and decreased after 4-7 years,⁶ which is in line with our findings, and might explain the relatively high remission rates after the first 5 years of the disease.

Our study was set up to identify predictors of remission and persistence of new onset asthma in adults. Two previously published studies on this topic^{9, 13} reported that there were differences between patients who remitted and not remitted (e.g. with respect to baseline FEV₁), but the number of patients with remitted asthma in those two studies was too low to properly analyze that point. Our study had enough remitted patients for more detailed statistical analysis and we found that airway hyperresponsiveness and nasal polyposis were strongly associated with asthma persistence but not lung function at baseline. In fact, all patients with nasal polyps showed asthma persistence. The importance of nasal polyposis in determining the persistence of asthma is a novel finding. Previous studies have shown a close association between upper airways involvement and asthma.^{27, 28} Allergic and non-allergic rhinitis have been shown to predict asthma onset,^{29, 30} and chronic rhinosinusitis is an important comorbid condition in patients with asthma.³¹ More importantly, chronic rhinosinusitis with nasal polyposis is associated with greater asthma severity and frequent exacerbations.³² Nasal polyposis as a predictor of chronicity and persistence of new onset asthma has not been reported before, although it is conceivable that asthma will persist as long as nasal polyps persist, since both are likely manifestations of the same underlying pathophysiological process.³³

Our study shows that apart from comorbid nasal polyps, the persistence of asthma is associated with the severity of the disease itself as reflected by increased bronchial responsiveness, although this association was six times weaker than for nasal polyps. Previous studies already reported an important role for bronchial hyperresponsiveness in the prognosis of asthma patients, in particular for predicting accelerated decline in FEV₁.³⁴ Our findings also fit in with data obtained in childhood asthma, showing that asthma persistence is strongly linked to greater frequency and severity of asthma symptoms, and more severe airway hyperresponsiveness.³⁵ However, unlike in children, atopic sensitization was not a predictor of persistence in our study of adults with new onset asthma.³⁶

The association of nasal polyposis with asthma persistence in our study was strong, yet, only a quarter of the patients with adult-onset asthma showed this condition. For patients without nasal polyposis, predictors of asthma persistence were less obvious. In a post-hoc evaluation of these patients, they appeared to be more frequently female and more often obese than patients with nasal polyps and to have poor asthma control (data shown in Table E I). In addition, these patients showed an increase in neutrophils over the years. This set of clinical characteristics fits in with a specific phenotype of adult-onset asthma, the so-called “obese female asthma phenotype” which has been identified in several large cluster analysis studies.^{3, 37, 38} and have been shown to have neutrophilic inflammation.^{39, 40} Apparently, patients with obesity associated asthma are not likely to achieve asthma remission, despite positive effects of weight loss in other studies.⁴¹

An alternative explanation might be the presence of chronic rhinosinusitis without nasal polyposis, which was observed in almost half of patients, and could have led to airway neutrophilia. This increase in non-type 2 inflammation suggests activation of Th17 and Th1 pathways, caused for instance by recurrent respiratory infections or exposure to environmental pollutants and thereby leading to persistent asthma.⁴²

What could be mechanisms leading to persistent asthma? Given the strong association between asthma persistence and nasal polyposis, it is likely that common causal mechanisms play a role in the development and persistence of both diseases. These include immune responses against fungi, bacteria, or bacterial enterotoxins leading to type 2 inflammation in both upper and lower airways.⁴³ Another factor that might induce and maintain both diseases is cigarette smoke. Cigarette smoking has been shown to be a risk factor for development of chronic airways disease.⁴⁴ In our study, the group of patients with persistent asthma and nasal polyps consisted of smokers and ex-smokers for more than 70%. A common mechanism could include cigarette smoke-induced inflammation in the airways, associated with nasal polyp formation and insensitivity to corticosteroids,⁴⁵ leading to an increased severity and persistence of nasal polyps and asthma.¹⁶

Almost two-thirds of the patients with polyps in our cohort had already undergone surgical treatment for nasal polyposis before the onset of asthma, suggesting that in these patients nasal polyposis had preceded the onset of asthma. However, despite this treatment, progression to persistent asthma had still occurred. Apparently, early treatment of nasal polyposis does not prevent asthma to develop or become chronic. Although adequate medical treatment of rhinitis has been shown to improve asthma control⁴⁶ our data suggest that surgical treatment of nasal polyposis is insufficient to prevent the development of persistent asthma.

The strength of our study was the prospective follow-up design and the extensive baseline characterisation of the patients. In addition, stringent criteria for asthma were used, consisting of physician's diagnosis confirmed by lung function measurements.¹⁵

A potential limitation of the study could be our definition of asthma remission. Clinical remission might not reflect pathophysiological remission, which includes normal airway responsiveness, and absence of airway inflammation. Previous studies have demonstrated on-going eosinophilic airway inflammation, airway hyperresponsiveness and airway remodelling in adolescents in clinical remission of atopic asthma.⁴⁷ Thus, subclinical asthma might have overestimated remission rates in our patients with adult-onset asthma. Another potential limitation of our study is that data from only 170 of 200 patients were available after 5 years. This could have introduced a selection bias, for example if the patients who were lost to follow-up had been the ones with an extensive smoking history. (Ex)smoking has been shown to worsen the prognosis of adult onset asthma,¹⁶ and might thereby also influence the chance of asthma remission. However, by comparing patients who were lost to follow-up with the rest of the cohort, we did not observe differences in smoking history.

Finally, the majority of patients were assessed at yearly intervals, which might have influenced the results of our study. However, we do not believe that this was the case, because these interval assessments were done by study investigators who were not linked to

the health care providers of the patients. The results of these assessments were not communicated to the health care providers, and did not lead to changes in treatment.

Our study has several clinical implications. Firstly, it provides useful indicators to identify patients with newly diagnosed asthma who are at risk of persistent disease. This new insight into the prognosis of asthma patients should lead to closer monitoring of these patients in order to improve asthma outcomes. Secondly, treatable traits in these patients including eosinophilic airway inflammation and nasal polyps should be addressed and treated.¹⁴ Biologicals targeting type 2 inflammation that have been shown to be effective in both conditions might be promising, although the effect of such treatment on the prognosis and persistence of asthma remains to be confirmed. Finally, all adults with newly diagnosed asthma should be evaluated for nasal polyposis, preferably by means of nasal endoscopy, because of their strong prognostic value. This advice should also be included in the GINA guidelines, where an examination of the upper airway is recommended in patients with severe asthma only.¹⁵

In conclusion, this study shows a relatively high remission rate in adult-onset asthma within the first 5 years of the disease, which is reassuring. However, a combination of nasal polyposis and moderate to severe bronchial hyperresponsiveness (PC_{20} -methacholine ≤ 1.0 mg/ml) at the time of asthma diagnosis reduces the chance of remission to almost zero. Recognition of these at risk patients at an early stage is necessary because both conditions are associated with impaired quality of life, reduced workplace productivity, and substantial medical treatment costs. Since eosinophilic airway inflammation seems to play a role in the persistence and chronicity of both asthma and nasal polyposis, this might offer options for early intervention with biologicals targeting key drivers of type 2 inflammation.^{48, 49}

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Table I. Baseline Characteristics of Patients With Persistent Asthma and Clinical Remission.

	Persistent asthma (n=143)	Clinical remission (n=27)	P-value
Female, %	57	44	0.243
Age, years *	50 ±14	44 ±15	0.039
BMI, kg/m ² *	28.2 ±5.2	26.5 ±5.0	0.132
Ex- or current smoker, %	58	48	0.342
Pack years #	4 (0-15)	1 (0-12)	0.266
ACQ-6 score *	1.34 ±0.92	0.89 ±0.67	0.026
Inhaled corticosteroid (ICS) use, %	81	70	0.212
ICS and second controller, %	64	52	0.248
Oral corticosteroid use, %	3	0	0.389
ICS dose (fluticasone equivalent) #	313 (250-500)	250 (0-250)	0.007
Asthma medication use, %	92	89	0.561
pre FEV ₁ % predicted *	93 17	95 16	0.709
pre FVC% predicted *	106 16	102 16	0.291
post FEV ₁ , % predicted *	100 ±17	99 ±14	0.785
post FVC% predicted *	108 16	103 17	0.107
FEV ₁ % reversibility #	5 (2-9)	4 (2-6)	0.134
post FEV ₁ /FVC, % predicted *	95 ±11	98 ±10	0.158
post DLCOcVA, % predicted *	98 ±15	96 ±17	0.562
post RV/TLC ratio, % predicted *	88 ±20	86 ±13	0.527
PC ₂₀ -Methacholine mg/ml #	2.7 (0.8-6.6)	5.8 (2.9-32)	0.003
Nasal polyps, %	25	0	0.004
GERD, %	39	42	0.763
Atopy, %	44	46	0.667
Obesity, %	33	19	0.138
Total IgE, kU/L #	68 (26-236)	59 (30-115)	0.497
FeNO, ppb #	21 (13-45)	29 (12-44)	0.698
Blood neutrophils, 10 ⁹ /L #	3.7 (3.0-4.6)	3.0 (2.7-4.0)	0.038
Blood eosinophils, 10 ⁹ /L #	0.17 (0.1-0.28)	0.15 (0.08-0.26)	0.601
Sputum eosinophils, % #	0.5 (0.1-3.8)	0.6 (0.2-1.5)	0.688
Sputum neutrophils, % #	71 (50-84)	82 (71-87)	0.143

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Pre: pre-bronchodilator. Post: post-bronchodilator. GERD: gastroesophageal reflux disease. Data are mean (±SD) indicated by *, median (interquartile range) indicated by # or percentage.

Table II. Comparison Between Baseline and 5-year Follow-up Data.

	Asthma persistence (n=143)				Remission (n=27)			
	Baseline	5 years	p-value		Baseline	5 years	p-value	
BMI, kg/m ² *	28.6 ±5.5	28.7 ±5.6	0.761	n=99	25.8 ±3.4	26.5 ±3.1	0.071	n=12
ACQ-6 score *	1.32 ±0.93	1.08 ±0.86	0.008	n=114	0.8 ±0.71	0.23 ±0.34	0.002	n=18
Inhaled steroid dose (fluticasone equiv) #	313 (250-500)	250 (0-500)	0.296	n=134	250 (0-250)	0 NA	<0.001	n=27
pre FEV ₁ % predicted *	94 ±17	95 ±19	0.379	n=92	93 ±14	93 ±13	0.852	n=12
post FEV ₁ % predicted *	100 ±17	101 ±19	0.262	n=96	97 ±12	98 ±12	0.678	n=12
FEV ₁ % reversibility #	5 (2-9)	5 (2-9)	0.581	n=95	4 (2-6)	5 (2-8)	0.438	n=12
post FEV ₁ /VC% predicted *	95 ±11	92 ±12	0.002	n=96	97 ±8	95 ±8	0.463	n=12
post DLCOcVA, % predicted *	100 ±15	100 ±16	0.785	n=96	98 ±18	100 ±15	0.373	n=12
post RV/TLC ratio, % predicted *	87 ±17	85 ±14	0.075	n=91	85 ±16	89 ±24	0.713	n=12
PC ₂₀ -Methacholine, mg/ml #	2.7 (0.8-6.6)	2.7 (1.2-16)	0.522	n=76	5.8 (2.9-32)	32 (5-32)	0.021	n=11
Total IgE, kU/L #	68 (26-236)	58 (21-177)	0.268	n=95	59 (30-115)	98 (33-168)	0.091	n=11
FeNO, ppb #	21 (13-45)	20 (12-35)	0.371	n=94	29 (18-44)	26 (14-31)	0.158	n=12
Blood neutrophils, 10 ⁹ /L #	3.7 (3-4.6)	3.4 (2.7-4.2)	0.369	n=96	3.0 (2.7-4)	3.5 (2.5-4.5)	0.388	n=12
Blood eosinophils, 10 ⁹ /L #	0.17 (0.1-0.28)	0.17 (0.12-0.27)	0.489	n=97	0.15 (0.08-0.26)	0.18 (0.1-0.27)	0.875	n=12
Sputum eosinophils, % #	0.8 (0.2-4.2)	0.6 (0.2-2.8)	0.200	n=45	0.6 (0.4-0.6)	0.6 (0.4-1.6)	0.180	n=2
Sputum neutrophils, % #	67 (50-77)	79 (66-91)	0.001	n=45	63 (49-63)	54 (34-70)	0.655	n=2

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502 Pre: pre-bronchodilator. Post: post-bronchodilator. Data are mean (±SD) indicated by * or median (interquartile range) indicated by #.

503 Figure 1. Consort diagram.

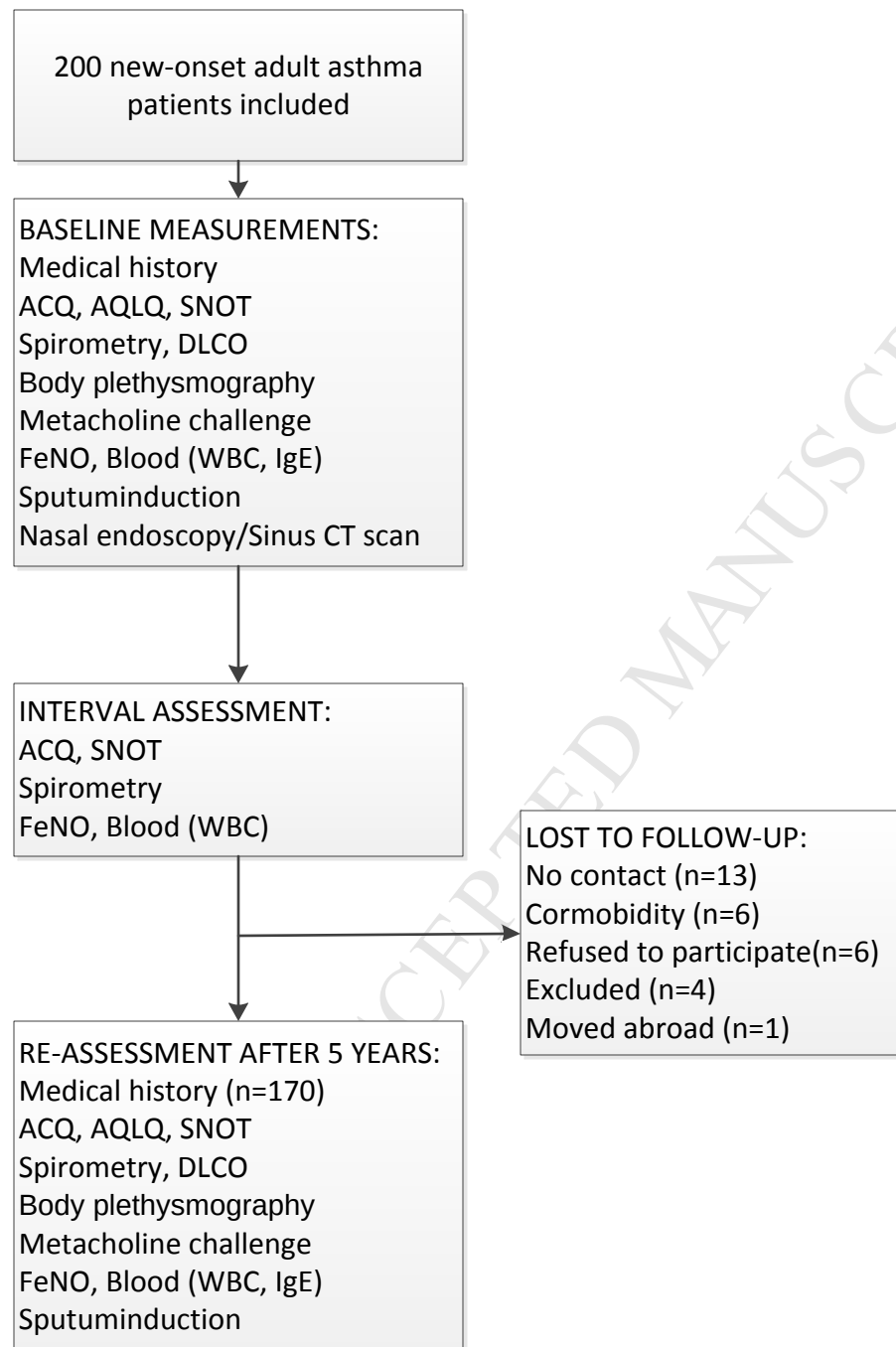
ACCEPTED MANUSCRIPT

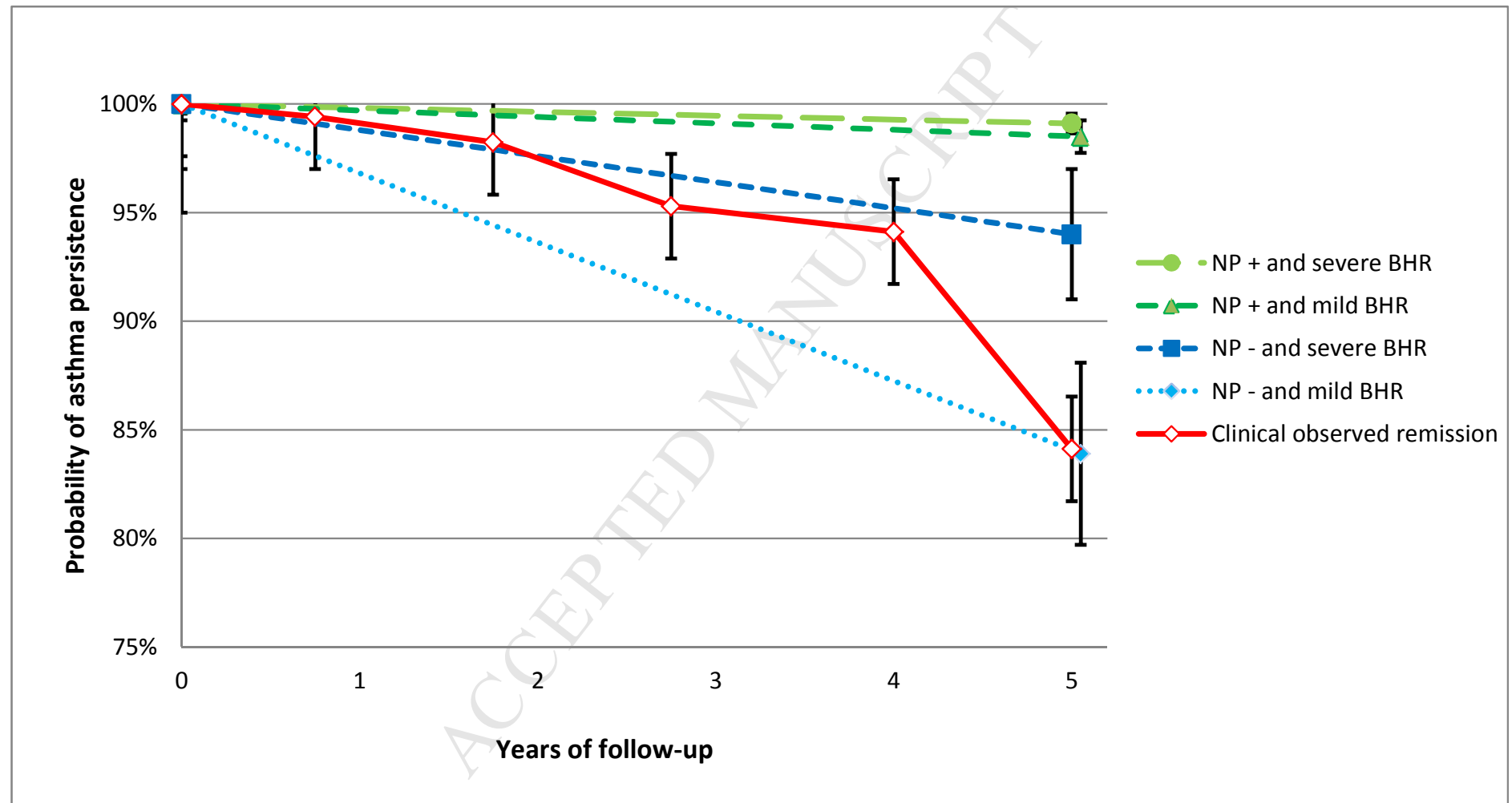
504 Figure 2. Probability of Asthma Persistence

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507 NP + : presence of nasal polyps. NP - : absence of nasal polyps. BHR: bronchial hyperresponsiveness. Dashed
508 lines represent the probability of asthma persistence calculated by the prediction model based on baseline
509 characteristics (NP and BHR). The continuous line shows the clinically observed percentage of patients
510 experiencing asthma remission in the cohort. **The error bars represent standard error.**





Online Repository material.

METHODS

Detailed inclusion and exclusion criteria: Two hundred patients with adult-onset asthma were recruited from the outpatient pulmonary clinics of one academic hospital and two secondary care hospitals in the Netherlands. All patients had to have a recent (<1 year) doctor's diagnosis of asthma. Adult-onset asthma was defined as asthma with an onset of the disease at >18 years of age. Asthma diagnosis was based on typical asthma symptoms and reversibility in FEV₁ of > 12% of predicted value and/or a positive inhaled methacholine provocation test (PC₂₀ < 8mg/ml).¹

Patients were excluded if they had a self-reported history of childhood asthma or other chronic respiratory diseases in childhood, frequent episodes of dyspnea as a child, or use of bronchodilator or other asthma medication in childhood.

Current smoking and ex-smoking were allowed. Patients with a smoking history of >10 pack years were included only if they showed reversibility in FEV₁ ≥12% of the predicted value, and had a normal CO diffusion capacity (DLCO >80%).

RESULTS

Table E I. Patients with Asthma Persistence, with and without Nasal Polyps.

	Absence of nasal polyps (n=107)		Nasal polyps (n=35)		p-value
		n		n	
Gender, % female	65	107	29	35	<0.001
Age, years *	48 ±14	107	56 ±14	35	0.004
BMI, kg/m ²	28.5 ±5.4	107	27.2 ±4.9	35	0.225
(Ex)smoker, %	53	107	71	35	0.059
Pack years #	2 (0-14)	106	8 (0-18)	35	0.132
ACQ-6 score *	1.40 ±0.94	100	1.12 ±0.81	33	0.133
Inhaled corticosteroid (ICS) use, %	79	107	85	34	0.450
ICS and second controller, %	62	107	69	35	0.463
Oral corticosteroid use, %	4	105	0	32	0.262
ICS dose (fluticasone equivalent) #	250 (125-500)	107	500 (250-500)	34	0.489
Any asthma medication baseline, %	92	107	94	34	0.632
pre FEV ₁ % predicted *	94 ±16	104	89 ±20	31	0.152
pre FVC% predicted *	105 ±16	102	106 ±18	29	0.985
post FEV ₁ % predicted *	100 16	107	99 19	35	0.707
post FVC% predicted *	108 ±16	107	109 ±17	35	0.726
FEV ₁ % reversibility #	5 (2-8)	104	5 (3-11)	34	0.143
post FEV ₁ /FVC% predicted *	96 ±11	107	92 ±12	35	0.056
Post DLCOcVA % predicted *	96 ±15	107	105 ±15	35	0.004
post RV/TLC ratio % predicted *	87 ±19	101	93 ±21	32	0.137
PC ₂₀ -Metacholine, mg/ml #	2.8 (0.9-6.4)	98	2.5 (0.5-10.6)	32	0.944
Nasal polyp surgery, %	NA	NA	66	35	NA
CRS, %	44	99	100	35	<0.001
GERD, %	42	107	29	35	0.155
Atopy, %	42	106	49	35	0.465
Obesity, %	37	107	20	35	0.058
Total IgE, kU/L #	60 (23-229)	101	79 (30-240)	34	0.396
FeNO, ppb #	16 13-31	101	39 (19-68)	34	<0.001
Blood neutrophils, 10 ⁹ /L #	3.7 2.9-4.8	103	3.8 (3.3-4.3)	35	0.994
Blood eosinophils, 10 ⁹ /L #	0.16 (0.1-0.24)	103	0.26 (0.2-0.35)	35	<0.001
Sputum eosinophils, % #	0.4 (0.1-1.6)	65	2.3 (0.9-8.9)	21	0.001
Sputum neutrophils, % #	72 (52-86)	65	68 (33-79)	21	0.188

Pre: pre-bronchodilator. Post: post-bronchodilator. GERD: gastroesophageal reflux disease. Data are mean (±SD) indicated by *, median (interquartile range) indicated by # or percentage.

26 Figure E 1. Asthma Remission Incidence Based on Different Definitions of Remission.

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29 No eosinophilia: sputum eosinophils < 3%.

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