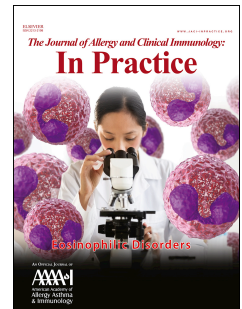


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Oliver Djurhuus Tupper, MD, Kjell Erik Julius Håkansson, MD, Charlotte Suppli Ulrik, MD, DMSc, Professor



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Remission and changes in severity over 30 years in an adult asthma cohort

Oliver Djurhuus Tupper, MD¹, Kjell Erik Julius Håkansson, MD¹, Charlotte Suppli Ulrik, Professor, MD, DMSc^{1,2}

¹ Department of Respiratory Medicine, Copenhagen University Hospital Hvidovre, Denmark

² Institute of Clinical Medicine, University of Copenhagen, Denmark

Running title: Remission and severity changes in an asthma cohort

Corresponding author full contact details:

Oliver D. Tupper, MD
Respiratory Research Unit Hvidovre
Dept. of Respiratory Medicine
Hvidovre University Hospital
Kettegård Alle 30
DK-2650 Hvidovre
E-mail: olivertupper@gmail.com
Phone: +45 38623825

Emails for co-authors: KEJH: kjell.erik.julius.haakansson@regionh.dk
CSU: csulrik@dadlnet.dk

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39 **ABSTRACT:**

40 **Background:** Long-term follow-up studies of adults with well-characterised asthma are sparse.

41 **Objective:** We aimed to examine long-term remission and change in disease severity over 30 years
42 in adults with asthma.

43 **Methods:** 125 individuals diagnosed with asthma between 1974-1990 at a Danish respiratory and
44 allergy clinic, based on history and objective assessments, were included. At follow-up (2017-19),
45 participants completed questionnaires and had spirometry, bronchodilator reversibility, airway
46 responsiveness and blood biomarkers measured. Based on these assessments, participants were
47 classified as having either active asthma, clinical remission (no symptoms or prescribed asthma
48 medication within the last year) or complete remission (FeNO <50 ppb, no bronchodilator
49 reversibility, no airway hyperresponsiveness and no airflow limitation). Changes in severity were
50 determined according to GINA guidelines based on symptom control and currently prescribed
51 medication.

52 **Results:** At follow-up, 25% (n=31) and 15% (n=19), respectively, had clinical and complete
53 remission. Our analyses showed that longer duration of symptoms before the initial assessment (OR
54 0.86, 95% CI 0.75—0.98) was associated with a lower chance of asthma remission. At follow-up,
55 30% had well-controlled asthma compared with none at baseline. Female sex, previous severe
56 exacerbation(s), and older age at baseline were associated with uncontrolled asthma at follow-up.
57 Blood-eosinophil count ($\geq 0.3 \times 10^9/l$) and prescribed ICS at baseline were associated with being
58 prescribed medium/high dose ICS at follow-up.

59 **Conclusion:** Despite 30 years of follow-up, asthma rarely remits in adults, especially in individuals
60 with longer duration and presumably more severe disease. Initial signs of pronounced disease
61 activity were associated with uncontrolled asthma at follow-up.

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64 **Highlights:**

65 **What is already known about this topic?**

66 Asthma remission rate is low in adults, but knowledge of factors associated with remission
67 is scarce.

68 **What does this article add to our knowledge?**

69 Over 30 years, remission of objectively verified asthma is associated with short disease
70 duration.

71 **How does this study impact current management guidelines?**

72 Early recognition, and treatment, of asthma in adults with preserved lung function, may
73 improve the likelihood of remission.

74
75 **Keywords:** Asthma, Remission, Severity, Adults, Eosinophils, Long-term

76
77 **Abbreviations:**

78 AHR = Airway Hyperresponsiveness

79 FeNO = Fractional exhaled nitric oxide

80 FEV1 = Forced expiratory volume in 1. second

81 FVC = Forced vital capacity

82 GINA = Global Initiative for Asthma

83 ICS = Inhaled Corticosteroid

84 PC₂₀ = The concentration of inhaled histamine that results in a 20% drop in FEV1

85 PEF = Peak expiratory flow

86 SABA = Short-acting β 2-agonist

87 TRAIL = Treatable traits in asthma, the impact on long-term outcome cohort.

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INTRODUCTION:

Despite dramatic improvements in asthma care, particularly with asthma medication, over the last half-century, asthma remains a cause of high societal and personal cost.^{1,2}

Long-term outcome of asthma has been described in multiple studies. However, the primary focus of these studies has been on the progression of childhood asthma into adulthood or epidemiologic studies with the diagnosis being based on self-reported disease or prescribed inhaler therapy.³⁻⁶ Findings seem to indicate a steady decline in the likelihood of remission as age increases, with remission of childhood asthma reported between 50-70%.^{4,7} In contrast, remission rates among adults have been found to be between 2-20%.⁸⁻¹⁴

Currently, long-term follow-up studies on adult asthma patients with well-characterised disease at baseline are sparse.¹⁵ The few published studies evaluating changes in disease severity (measured by symptom burden, GINA treatment step and FEV₁) over time, show conflicting results. Three studies^{8,12,16} found that the majority of patients had declining severity between baseline and follow-up visits. On the other hand, a study by de Marco et al.¹¹ found that disease severity was mostly unchanged at follow-up. Adults with asthma consist of a significant proportion of the total asthma population, with a reported prevalence between 6-10%.¹⁷ In the USA, the CDC reports an equal prevalence of asthma between children and adults.¹⁸ The individual disease burden has been reported as being higher in adults than in children.⁶

Therefore, additional large long-term follow-up studies of adults with well-defined asthma are needed to understand remission and changes in severity better.¹⁵ The present study aimed to examine the frequency of remission and change in disease severity for adults with asthma.

113 Additionally, we aimed to explore whether any factors potentially may be associated with remission
114 or disease severity long-term.

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METHODS:

The present study is a longitudinal cohort study of individuals with well-characterised asthma. Individuals referred for diagnostic workup or management of asthma at a Danish respiratory outpatient clinic were consecutively recruited, provided the diagnosis of asthma was verified. These individuals will be referred to as the treatable traits in asthma, impact on long-term outcome (TRAIL) cohort. The follow-up part of the study consisted of a research prompted visit, where all still living individuals in the TRAIL cohort were invited to a follow-up visit. The study was approved by the ethical committee for the Capital Region of Denmark (H-17025043) and The Danish Data Protection Agency (2013-41-2618).

Baseline data

The patient cohort and methods used at baseline have been described previously by Ulrik et al.¹⁹ All baseline data were gathered from patient records. The cohort consists of all persons diagnosed with and followed for asthma between 1974-1990, at Frederiksberg Respiratory and Allergy Clinic, Denmark. Persons included were ≥ 13 years old at baseline. The diagnosis of asthma was made by a respiratory medicine specialist. Individuals were determined as having asthma if they had a typical history (wheezing or attacks of breathlessness; chest tightness; cough triggered by exercise, exposure to allergens or irritants or respiratory infections) and one or more of the following asthma tests:

- 1) FEV_1 reversibility $> 15\%$ (and an absolute increase of > 150 ml) after a standard dose of short-acting β_2 -agonist (SABA), oral corticosteroid or both (30 mg/d) for 14 days.²⁰
- 2) Positive histamine provocation test, with the provocative concentration of histamine that results in a 20% drop in FEV_1 (PC_{20}) ≤ 8 mg/ml.²¹
- 3) Diurnal variability in peak expiratory flow (PEF) rate $> 20\%$ and absolute variation > 100 L/min.^{22,23}

A thorough history was obtained during the first visit to the respiratory outpatient clinic. Blood eosinophil count was measured three times for each patient, the most abnormal result was recorded.²¹ Forced expiratory volume in 1. second (FEV₁ and forced vital capacity (FVC) were measured using a dry-wedge bellows spirometer (Vitalograph®). The best of three technically acceptable readings were recorded. Fifteen minutes after inhalation of a standard dose of SABA FEV₁ was measured again. FEV₁ reversibility was calculated as (FEV₁ after – FEV₁ before)/FEV₁ before). Total serum IgE was determined by paper radio-immunosorbent test (Pharmacia). Skin prick test was performed with standard aeroallergens. All participants went through the same diagnostic algorithm for adults referred for suspected asthma.

Follow-up visit

All persons from the baseline population still alive in 2017-2019 were invited by letter to a follow-up visit at Hvidovre Hospital, Denmark. A reminder letter was sent after one month if no response to the initial letter was received. Anyone who accepted the invitation was included. Figure 1 shows a flowchart of the invitation process. Before the follow-up visit participants were asked whether they had asthma, previously had asthma or never had asthma.

The follow-up visit consisted of a comprehensive examination of their current asthma status, see online repository for a full description of procedures:

- 1) Questionnaires. GINA symptoms control (described below) and questions described in online repository.
- 2) Current inhaler medication (cross-referenced with currently prescribed medication in the Danish common medicine card).
- 3) Blood tests: Eosinophils and total IgE
- 4) Skin prick test was performed according to the method described by Bousquet et al ²⁴
- 5) Spirometry and β_2 -reversibility.^{25,26} Significant reversibility was defined as an absolute increase in FEV₁ of ≥ 200 ml and $\geq 12\%$ increase in relative volume, after 0.4 mg salbutamol.

6) Fractional exhaled Nitric Oxide (FeNO)²⁷ was measured with EcoMedics CLD 88sp analyser and DENOX 88. The mean value of the two measurements (flowrate 50 ml/min) was recorded.

7) Bronchial challenge test.²⁶ Participants inhaled stepwise accumulating doses until either: 635 mg was inhaled with no significant change in FEV₁, a 15% drop in FEV₁ from the baseline value or a 10% drop between two doses. A positive test (PD15 $\leq$ 635 mg) was defined as airway hyperresponsiveness (AHR).

The methods for β_2 -reversibility (12% and 200 ml instead of 15% and 150 ml) and bronchial challenge test (mannitol instead of histamine) differed between follow-up and baseline, this difference reflects current clinical practice in asthma diagnosis.

Remission of asthma

Clinical remission was defined as the following:

- 1) No asthma symptoms within the last year (wheeze, dyspnoea, chest tightness, cough and/or sputum).
- 2) No currently prescribed and self-reported use of asthma medication within the last year.

The following factors, together with the factors defining clinical remission, were defined as complete remission:

- 1) FeNO $\leq$ 50 ppb.²⁸
- 2) No bronchodilator reversibility.
- 3) No AHR.
- 4) Spirometry with FEV₁ $\geq$ 80% pred. and FEV₁/FVC ratio $\leq$ 0.70. If not the only factor.

Changes in asthma control and treatment intensity

As there is no gold standard for measuring asthma severity in epidemiological studies,²⁹ we evaluated severity based on two surrogate markers at baseline and follow-up, separately. As GINA symptom control was not completed at baseline, it was completed retrospectively from the patient records, as all relevant information was available there:

- a) GINA 2017³⁰ symptom control level consists of four yes or no questions: (1) Day time symptoms more than twice/week? (2) Any night waking due to asthma? (3) Reliever needed more than twice/week? (4) Any activity limitation due to asthma? The level of asthma control is based on the number of questions answered yes:
 - 1) Well-controlled: 0.
 - 2) Partly controlled: 1—2.
 - 3) Uncontrolled: 3—4.
- b) Asthma treatment level
 - 1) Reliever only
 - 2) Low-dose inhaled corticosteroids (ICS), 200—400 ug budesonide (or equivalent)
 - 3) Medium-dose ICS, >400—800 ug budesonide (or equivalent)
 - 4) High-dose ICS >800 ug budesonide (or equivalent) and/or maintenance oral corticosteroids

Statistics

The following factors, recorded at baseline, potentially being predictors of disease remission and change in severity were examined: Age, sex, childhood- or adulthood-onset, duration of symptoms before baseline, FEV₁ % predicted, FEV₁/FVC ratio, blood eosinophils, total IgE, positive or negative skin prick test, baseline asthma medication, airway hyperresponsiveness to inhaled histamine and tobacco exposure. There were missing data on the histamine challenge test (n=34, 27%), missing values were analysed by multiple imputation. As there is no current consensus on

blood eosinophil levels, we stratified by three different measures: <0.09 , ≥ 0.09 to ≤ 0.4 , or > 0.4 ; above or below 0.3; and above or below $0.15 \times 10^9/l$.³¹⁻³³

Baseline differences between the groups with and without active asthma were compared using student's t-test, Mann-Whitney U-test and Fisher's exact test. To analyse baseline differences between asthma control groups one-way ANOVA, Kruskal-Wallis test and Fisher's exact test were used. Changes in treatment level and GINA symptom control between baseline and follow-up were compared using paired sample t-test. Binomial logistic regression analyses were performed to examine factors associated with remission, asthma control and treatment at follow-up. Variables with a p-value < 0.2 in the bivariate analyses were included in the multivariable model. A two-tailed p-value < 0.05 was determined as significant. Statistical analyses were performed using SAS Enterprise Guide, version 7.15 (SAS Institute Inc. Cary, NC, USA). Additional statistical analyses are described in the online repository.

RESULTS:

One-hundred-twenty-five individuals (of 616 alive) accepted participation in the follow-up visit (Figure 1), with mean follow-up time 33.3 years (3.6 SD). At baseline, participants and non-responders only had insubstantial differences in age and FEV₁ (L) (Table 1) and, therefore, the 125 participants are assumed to be representative of the entire (living) cohort.

Remission

Before follow-up, 77 (62%) reported current asthma, 36 (29%) previous asthma and 12 (9.6%) stated that they never had asthma. At follow-up 31 (25%) had clinical remission. The discrepancy between response before and during the follow-up visit is due to systematic questioning at the follow-up visit, as this revealed symptoms that participants had not connected to their previous diagnosis of asthma over 30 years ago.

Based on the previously defined criteria, 106 (85%) showed signs of active asthma, 50% of participants fulfilled at least three, and 79% fulfilled at least two criteria for active asthma. The eight participants that only met one criterion were: Five had AHR, and two had significant bronchodilator reversibility. One participant had no symptoms and only reduced lung function and was defined as in complete remission. Eighteen (15%) fulfilled none of the criteria for active asthma criteria and, by that, had complete remission, this equates to a yearly remission rate of 0.46%.

Remission rates were 13% for those with onset before age 18 (N=47) and 17% for age 18 and above (N=78). Participants in remission had better lung function, and less β_2 -reversibility at baseline (Table 2). Likewise, at follow-up, individuals in remission had better lung function, and lower blood eosinophils compared with individuals with active asthma (Table E1).

Duration of symptoms before baseline (OR 0.89, 95% CI 0.79—0.99) was inversely related to remission in the multivariable model (Table 3). In addition, the effects of baseline FEV₁ % predicted (OR 1.05, 95% CI 1.00—1.10), blood eosinophils (OR 0.2, 95% CI 0.04—1.71), and being prescribed any dose of ICS at baseline (OR 0.34, 95% CI 0.11—1.04) are likely to be meaningful predictors of remission, but the relatively small sample size lacked statistical power for effects of this size to be statistically significant.

Changes in asthma control and treatment intensity

Only participants who were classified as having active asthma (N=106) at follow-up were included in the following analyses.

Based on GINA symptom control, at baseline 49 (46%) were partially controlled, and 57 (54%) were uncontrolled. At follow-up, 33 (31%) were well controlled, 49 (46%) were partially controlled, and 24 (23%) were uncontrolled. Figure 2 shows changes in GINA symptom control score from baseline to follow-up. At follow-up 49 were partially uncontrolled, only half of them were prescribed ICS, 20% had no treatment at all, and about a third were treated with SABA only. There was a mean change in GINA symptom control score of -0.63 (0.87 SD) and median change of -1 (interquartile range 1) ($p < 0.001$), corresponding to an improvement in symptom scores between baseline and follow-up visit. Table 4 compares baseline factors stratified by symptom control at follow-up. Female sex (OR 5.89, 95% CI 1.58—22.0), increasing age (OR 1.09, 95% CI 1.01—1.17) and previous asthma exacerbations (OR 5.81, 95% CI 1.40—24.1) were associated with uncontrolled disease at follow-up (Table E2 in online repository). Additionally, there appeared to be a clinically meaningful association between a higher FEV₁/FVC ratio and lower odds of uncontrolled disease (OR 0.94, 95%CI 0.87-1.01), although this association lacked the power to be described as statistically significant.

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The prescribed treatment for asthma at the baseline and follow-up is given in Fig. 3. There was no statistically significant ($p = 0.053$) decrease in the treatment level between baseline and follow-up visit. Additionally, this difference was not clinically meaningful, with a mean change of -0.28 (1.49 SD) and median 0 (IQR 2) in treatment levels. Factors associated with medium or high dose ICS at follow-up were blood eosinophils $\geq 0.3 \times 10^9/l$ (OR 3.27 , 95% CI 1.10 — 9.72) and prescribed maintenance ICS (OR 3.34 , 95% CI 1.18 - 9.45) at any dose (Table E3 in online repository).

DISCUSSION:

This longitudinal study of 125 adults with asthma showed that after an average of 33 years, 25% had clinical remission, and 15% had complete remission of asthma. We found that duration of symptoms before baseline were predictors of remission at the follow-up visit. Overall there was a slight improvement in severity based on GINA symptom control score and treatment level. Previous severe exacerbations and female sex at baseline was a predictor of uncontrolled asthma at follow-up. Having ICS already prescribed and higher blood eosinophils at baseline were associated with medium or high dose ICS at follow-up.

Our cohort consists primarily of persons with adult-onset (≥ 18 years) asthma (62%), but a significant percentage (38%) of the TRAIL cohort had childhood-onset asthma (< 18 years). As previous studies have shown, there appears to be an inverse relationship between age of asthma debut and likelihood of remission, i.e. as age increases the likelihood of asthma remission decreases.¹³ However, in the TRAIL study, the persons with asthma debut before age 18 had a similar remission rate to those aged 18+; this could be because the persons with childhood-onset asthma were included at age 15+ at the baseline study visit and therefore, already had persistent asthma. Additionally, persons with childhood-onset asthma had asthma a median of 16 years at the time of baseline visit, while the persons with adult-onset had asthma for a median of three years. Indeed, this is supported by our finding that the duration of asthma symptoms before the baseline visit was inversely related to the odds for long-term remission after adjusting for age and lung function. This association has been previously shown in a large cross-sectional study, that found those in remission had a much shorter duration of disease (5.6 vs 16.1 years) compared with participants with active asthma.³ Sözüner et al¹⁰ similarly found the length of disease to be shorter among those in remission in a seven-year adult-onset asthma cohort study.

In the multivariable model, while we lacked statistical power, there was a potentially clinical meaningful association showing that the higher FEV₁ % pred. was at baseline, the better odds were

for remission. FEV₁ being associated with remission is supported by two cohort studies that found those in remission had a better FEV₁ at baseline than those that had active asthma when comparing groups without adjusting for other factors.^{8,9} Finally, while again lacking statistical power to show an association, ICS also appeared to have a clinically meaningful association with lower odds of remission. Having ICS already prescribed at baseline is likely a reflection of these individuals having more severe disease and, as has been reported previously, there appears to be an association between milder disease and higher remission rates.¹⁴

Our reported remission rate is among the highest reported in available studies on adult asthma.^{8-10,12,13,36} However, due to considerable differences in follow-up time, a yearly remission rate seems more appropriate to allow comparison. We found a yearly remission rate of 0.46%; this is similar to those found in other adult asthma cohort studies by Tuomisto et al¹² of 0.17%, Panhuysen et al⁹ of 0.44% and Rönmark et al³⁷ of 0.6%. Contrast this with findings by Westerhof et al. who found a yearly remission rate of 3.2%.¹³ The higher remission rate is probably because they included only persons with new-onset asthma and as indicated by the present study, the duration is an essential factor in asthma remission, and that possible remission is highest the first years after diagnosis.³ A population study found a remission rate in adults with asthma of 2%, however, unlike the previously mentioned studies, remission was based on self-reported presence or absence of asthma.¹⁴

Our criteria for remission was complete remission, as suggested by some studies clinical remission alone is not indicative of no disease activity.³⁸ We chose to allow a single marker to be indicative of active asthma, as all participants previously had been diagnosed based both on history and objective findings. The one exception was non-reversible airflow limitation, which could not stand on its own,

413 as this could be a consequence of previous airway remodelling or smoking, not necessarily a
414 consequence of active airway inflammation.

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416 At baseline, participants were not optimally controlled, as they were all referred for either diagnosis
417 or treatment optimisation; this is reflected by their GINA symptom control scores where zero
418 participants were well controlled. We found that overall there was a slight improvement in
419 symptom control. However, only a third were well controlled at the TRAIL study visit. Sözüner et
420 al¹⁰ and Tuomisto et al¹² showed a similar 22% and 30% of participants with uncontrolled and 29%
421 and 36% with partially controlled disease, respectively. Both studies defined asthma after diagnosis
422 at a specialist centre and showed a slight improvement overall in symptom control. However, the
423 lack of control seen in these three studies rather than reflecting more severe asthma is likely more a
424 reflection of lack of proper follow-up, treatment optimisation or adherence. Our finding that female
425 sex, higher age and previous exacerbations was associated with uncontrolled asthma is in line with
426 previous studies.³⁹

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428 Our other measure of severity was daily prescribed dose of ICS or OCS at follow-up. However,
429 treatment level is only a surrogate measure as explained previously, no patients at baseline, and
430 very few at follow-up were inappropriate treatment. This measure was chosen due to a current lack
431 of viable options to track severity in epidemiological studies.²⁹ High blood eosinophils at baseline
432 were associated with being prescribed medium or high dose ICS at follow-up. Tuomisto et al.¹²
433 found a blood eosinophil count $>0.44 \times 10^9/l$ was predictive of uncontrolled asthma at follow-up 12
434 years later. Being prescribed any dose of maintenance ICS already at baseline was associated with a
435 higher likelihood of medium or high dose ICS at follow-up. This has to our knowledge not been
436 reported previously, but it may merely be severe disease at baseline tracking up through time.
437 However, using ICS dosage alone is not a comprehensive measure of severity, as it does not

account for current symptom control and signs of paraclinical disease activity. Overall with results from the TRAIL study and the five other studies on adult asthma severity, it appears that long-term adult asthma is slightly better controlled, yet have largely unchanged treatment levels.^{8,11,12,16,40}

A clear strength of the TRAIL study is the amount of information available at baseline, and that asthma diagnoses were based both on history and objective findings evaluated by a respiratory physician, both at baseline and at the follow-up visit.

The largest limitation is the high number of non-responders. We have sought to account for this in table 1, with no significant differences between responders and non-responders in available baseline measures. However, we cannot rule out measures being significant when scaled up to the entire asthma population or whether there are differences in any unaccounted variables that impact remission. This may limit the external validity of this study. Additionally, it cannot be ruled out that individuals with asthma in remission were less inclined to participate in the study. However, 38% of participants reported asthma in remission or never having asthma. Furthermore, the remission rate in our study matches those of other remission studies.

Ideally, we would have had several additional visits between baseline and the TRAIL visit, to allow us to evaluate the persistence of remission, as it has been previously shown that the remission rate is not constant and many have periods of remission that later relapses.⁴¹ This was shown in a cohort study that found 22 persons (6 of whom had symptoms/exacerbations at follow-up) who were previously found to be in remission showed positive bronchial challenge test one year later.³⁶

Due to the small sample size, there are a relatively low number of events per variable, particularly for predictors of remission. Therefore, the results from predictor analysis cannot stand on their own but should be compared with similar studies.

Adult asthma rarely remits, particularly for patients with longer disease duration. Overall disease severity improves slightly long-term, but patients with previous severe exacerbations, high blood eosinophils, and already prescribed daily ICS are more likely to have poor long-term control and more severe disease.

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Figures

Figure 1 Flow-chart for inclusion in the TRAIL study. Shows persons eligible for the follow-up visit and how many declined or gave no response.

Figure 2. Shows participants change in GINA symptom control score between baseline and follow-up visit with a decline in GINA step reflecting an improvement in symptom control.

Figure 3 – Shows changes in levels of prescribed asthma medication (ICS, Saba alone or none) between baseline and follow-up in 125 adults.

Low dose ICS =200—400 ug/day, Medium=400—800 ug/day, High=800-1600 ug/day all in budesonide equivalent doses.

TABLES:

Table 1. Characteristics for the TRAIL cohort at the time of enrolment, stratified according to responder status at the follow-up visit.

Non-responders defined as being alive at the time of follow up but declined the invitation.

		Baseline		p-value
		Non-responders N=359	Responders N=135	
Sex, women, n (%)		298 (61)	75 (60)	0.919
Age (y), mean (SD)		31 (11)	29 (9)	0.010
Smoking	Ever smokers, n (%) ^a	91 (23)	34 (27)	0.058
	Pack yrs, median (Q ₁ —Q ₃) ^b	6.5 (3—11)	4 (2—12)	0.144
Asthma duration (yrs), median (Q ₁ —Q ₃)		4 (1—11)	4 (2—12)	0.396
Previous exacerbation, n (%)		147 (16)	26 (21)	0.154
Lung Function	FEV ₁ , L, mean (SD)	3.27 (0.78)	3.43 (0.69)	0.042
	FEV ₁ , % pred, mean (SD)	88 (15)	90 (14)	0.161
	FEV ₁ /FVC, mean (SD)	0.77 (9)	0.79 (8)	0.093
Asthma Tests	Bronchodilator reversibility, median (Q ₁ —Q ₃)	17 (15—26)	18 (15—27)	0.664

Daily doses of SABA ^c , median (Q ₁ —Q ₃)	2 (2—5)	2 (2—4)	0.068
Blood eosinophils, x10 ⁹ /l, median (Q ₁ —Q ₃)	0.34 (0.21—0.57)	0.34 (0.22—0.58)	0.559

a=Current and ex-smokers.*b*=for ever smokers. *c*=either doses of 100 ug salbutamol inh. or. 5 mg tbl. *SD*= Standard

Deviation. Q₁—Q₃=25th—75th percentile.

Table 2 Characteristics at baseline (i.e. time of enrolment into the TRAIL-cohort) stratified

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		Active asthma (N=106)	Asthma Remission (N=19)	p-value	rdin
Sex, women (%)		61 (58)	14 (74)	0.21	g to
Age at inclusion, mean (SD)		29 (8.3)	27 (10.3)	0.437	asth
Never smokers (%)		77 (73)	14 (74)	1.00	ma
Symptom debut before baseline, years, median (Q ₁ —Q ₃)		4.5 (2—14)	3 (1—6)	0.998	statu
GINA symptom control	Well-controlled	0	0	0.629	s at
	Partially controlled	49 (46)	10 (53)	0.63	follo
	Uncontrolled	57 (54)	9 (47)	0.630	w-up
Adult-onset, age ≥18 years, n (%)		65 (61)	13 (68)	0.62	(curr
Previous exacerbation, n (%)		23 (22)	3 (12)	0.76	ent
Lung Function	FEV ₁ , litre, mean (SD)	3.42 (0.70)	3.47 (0.70)	0.981	activ
	FEV ₁ , percent predicted, mean (SD)	89.2 (13)	95.7 (10)	0.622	e
	FEV ₁ /FVC ratio, %, mean (SD)	79 (7.8)	80 (6.1)	0.633	asth
Asthma Tests	Bronchodilator reversibility, median (Q ₁ —Q ₃)	18 (15—27)	16 (9—21)	0.634	ma
Blood	Blood eosinophils, x10 ⁹ /l, median (Q ₁ —Q ₃)	0.34 (0.22—0.61)	0.33 (0.15—0.48)	0.31	
	IgE Total, IU/l	170 (49—388)	155 (23—418)	0.48	
Asthma Medication	Daily ICS, ug ^a , median (Q ₁ —Q ₃)	200 (0—600)	0 (0—1000)	0.636	
	Daily SABA puffs, median (Q ₁ —Q ₃)	2 (2—4)	2 (1—5)	0.967	
Negative Skin prick test, n (%)		29 (27)	6 (32)	0.788	

vs. asthma in remission).

a=Budesonide equivalent doses. *SD*= Standard deviation. Q₁—Q₃=25th—75th percentile.

Table 3 – Baseline factors associated with complete asthma remission, based on bivariate and multivariable analyses.

		Bivariate model			Multivariable model		
Baseline factors		Odds Ratio	95% CI	P-value	OR	95% CI	P-value
Sex, female		2.07	0.64—6.15	0.193	1.82	0.57—5.82	0.315
Age at baseline, years		0.97	0.91—1.03	0.349	-	-	-
Adult-onset ^a		0.73	0.26—2.08	0.557	-	-	-
Ever smoker ^b		0.95	0.31—2.89	0.925	-	-	-
Symptom debut before baseline, years		0.91	0.83—0.99	0.048	0.89	0.79—0.99	0.034
GINA symptom control	Well-controlled	-	-	0.607	-	-	-
	Partially controlled	1.00	-		-	-	
	Uncontrolled	0.77	0.29—2.06		-	-	
Previous asthma exacerbation		0.68	0.18—2.53	0.561	-	-	-
Lung Function	FEV ₁ % predicted	1.04	0.99—1.08	0.056	1.05	1.00—1.10	0.061
	FEV ₁ /FVC ratio	1.02	0.95—1.09	0.594	-	-	-
Asthma Tests	β ₂ -reversibility	0.98	0.94—1.02	0.340	-	-	-
	AHR ^c	1.08	0.87—1.34	0.498	-	-	-
	Peak flow variability	1.03	0.99—1.07	0.201	-	-	-
Blood	Eosinophils	0.31	0.05—1.84	0.198	0.24	0.04—1.71	0.155
	IgE total	0.99	0.99—1.00	0.442	-	-	-
Asthma Medication	ICS prescribed at baseline	0.46	0.17—1.24	0.123	0.34	0.11—1.04	0.058
	Daily β ₂ dose ^d >2	0.82	0.30—2.19	0.684	-	-	-
Negative skin prick test		0.82	0.28—2.35	0.706	-	-	-

a=age 18 or above. b=Current or ex-smoker. c=Airway Hyperresponsiveness to histamine (PC20). d=either doses of 100 ug salbutamol inh. or. 5 mg terbutalin tbl.

Table 4

Baseline characteristics among participants in the follow-up study stratified according to level of asthma control at follow-up (as defined by GINA).

		Well controlled (n=33)	Partially controlled (n=49)	Uncontrolled (n=24)	P-value
Sex, Women, n (%)		15 (45)	28 (57)	18 (75)	0.088
Age at baseline, mean (SD)		27 (6.4)	29 (8.7)	32.8 (8.7)	0.026
Adult-onset ^a , n (%)		21 (57)	37 (63)	7 (70)	0.763
Yrs since debut, median (Q ₁ -Q ₃)		4 (1—11)	5 (2—15)	5 (2—16)	0.400
Ever smoker, n (%)		11 (21)	14 (29)	9 (38)	0.317
Previous exacerbation, n (%)		11 (21)	7 (14)	8 (33)	0.154
Pulmonary Function	FEV ₁ % pred. mean (SD)	92 (12.7)	88 (14.8)	88 (13.9)	0.462

	FEV ₁ /FVC ratio, mean (SD)	80 (6.6)	79.6 (7.9)	74.8 (8.4)	0.019
Asthma Tests	Bronchodilator reversibility (%), median (Q ₁ -Q ₃)	17 (16—21)	20 (16—30)	17 (10—26)	0.172
	AHR ^b , mg/ml, median (Q ₁ -Q ₃)	2.2 (1.03—4.35)	2.2 (1.34—4.89)	2.2 (1.8—4.5)	0.966
	Peakflow variability (%), median (Q ₁ -Q ₃)	21 (15—24)	23 (16—30)	25 (16—31)	0.361
Asthma Medication	ICS prescribed, n (%)	17 (52)	35 (71)	13 (54)	0.147
	Daily SABA ^c > 2	7 (21)	26 (54)	9 (38)	0.015
Total IgE IU/l, median (Q ₁ -Q ₃)		140 (42.5—390)	185 (54.0—456)	215 (65.0—335)	0.791
Blood Eosinophils x10 ⁹ /l, median (Q ₁ -Q ₃)		0.39 (0.26—0.68)	0.33 (0.22—0.57)	0.33 (0.19—0.60)	0.527

651 *a*=age over 18 years. *b*=Airway Hyperresponsiveness to histamine, 34 missing. *c*=doses of 100 ug salbutamol inh.

652 *SD*=Standard Deviation. Q₁-Q₃=25th—75th percentile.

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Table E2 - Baseline characteristics associated with uncontrolled asthma at the follow-up, compared with participants with either well-controlled or partially controlled asthma at follow-up.

		Bivariate model			Multivariable model		
Baseline factors		Odds Ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Sex, female		2.7	0.98—7.56	0.055	5.89	1.58—22.0	0.008
Age, years		1.07	1.09—1.23	0.022	1.09	1.01—1.17	0.027
Adult-onset ^a asthma		1.35	0.52—3.51	0.542	-	-	-
Years since symptom debut		1.02	0.97—1.07	0.525	-	-	-
GINA symptom control	Well-controlled	-	-	-	-	-	-
	Partially controlled	1.00	-	-	-	-	-
	Uncontrolled	1.27	0.51—3.29	0.612	-	-	-
Ever smoker ^b		1.86	0.71—4.90	0.209	-	-	-
Previous severe exacerbation		2.43	0.87—6.77	0.090	5.81	1.40—24.1	0.016
Lung Function	FEV ₁ % pred.	0.99	0.96—1.02	0.540	-	-	-
	FEV ₁ /FVC ratio	0.92	0.86—0.98	0.008	0.94	0.87—1.01	0.083
Asthma tests	Bronchodilator reversibility	0.99	0.96—1.03	0.738	-	-	-
	AHR ^c , mg/ml	0.98	0.80—1.21	0.872	-	-	-
	Peakflow variability	1.04	0.98—1.09	0.179	1.04	0.98—1.11	0.207
Asthma Medication	ICS prescribed ^d	0.68	0.27—1.71	0.415	-	-	-
	Daily β_2 dose ^e > 2	1.44	0.58—3.58	0.436	-	-	-
Blood Eosinophils		0.74	0.23—2.33	0.601	-	-	-
Total IgE		1.00	1.00—1.00	0.724	-	-	-
Skin prick test, negative		1.17	0.41—3.32	0.768	-	-	-

a=age ≥ 18 years. b=Current or ex-smoker. c=Airway hyperresponsiveness to histamine. d=any dose prescribed at baseline e=either doses of 100 ug salbutamol inh. or. 5 mg tbi terbutalin.

1 Table E1 – Characteristics of participants at the follow-up visit stratified according to current

2 asthma

		Active asthma (N=106)	Asthma Remission (N=19)	p-value	3 status (current active asthma vs. asthma in remissi on).
					4
Sex, women (%)		61 (58)	14 (74)	0.214	5
Age at follow-up, mean (SD)		62 (8.4)	59 (9.5)	0.328*	6
Never smokers (%)		48 (45)	9 (47)	0.829*	7
GINA symptom control	Well-controlled	33 (31)	19 (100)	0.952*	8
	Partially controlled	49 (46)	0		
	Uncontrolled	24 (23)	0		
Lung Function	FEV ₁ , litre, mean (SD)	2.40 (0.76)	2.84 (0.88)	0.007*	9
	FEV ₁ , percent predicted, mean (SD)	83 (20)	99 (18)	0.019*	
	FEV ₁ /FVC ratio, %, mean (SD)	0.68 (0.10)	0.77 (0.06)	<0.001*	
Asthma Tests	Bronchodilator reversibility, median (Q ₁ —Q ₃)	5 (1.69—10.6)	2 (-0.73 to 5.14)	0.018*	10
Blood	Blood eosinophils, x10 ⁹ /l, median (Q ₁ —Q ₃)	0.20 (0.11—0.30)	0.11 (0.10—0.20)	0.018*	11
	IgE Total, IU/l, median (Q ₁ —Q ₃)	90 (29—246)	41 (7—122)	0.257*	12
Negative Skin prick test, n (%)		24 (23)	4 (21)	0.578*	13

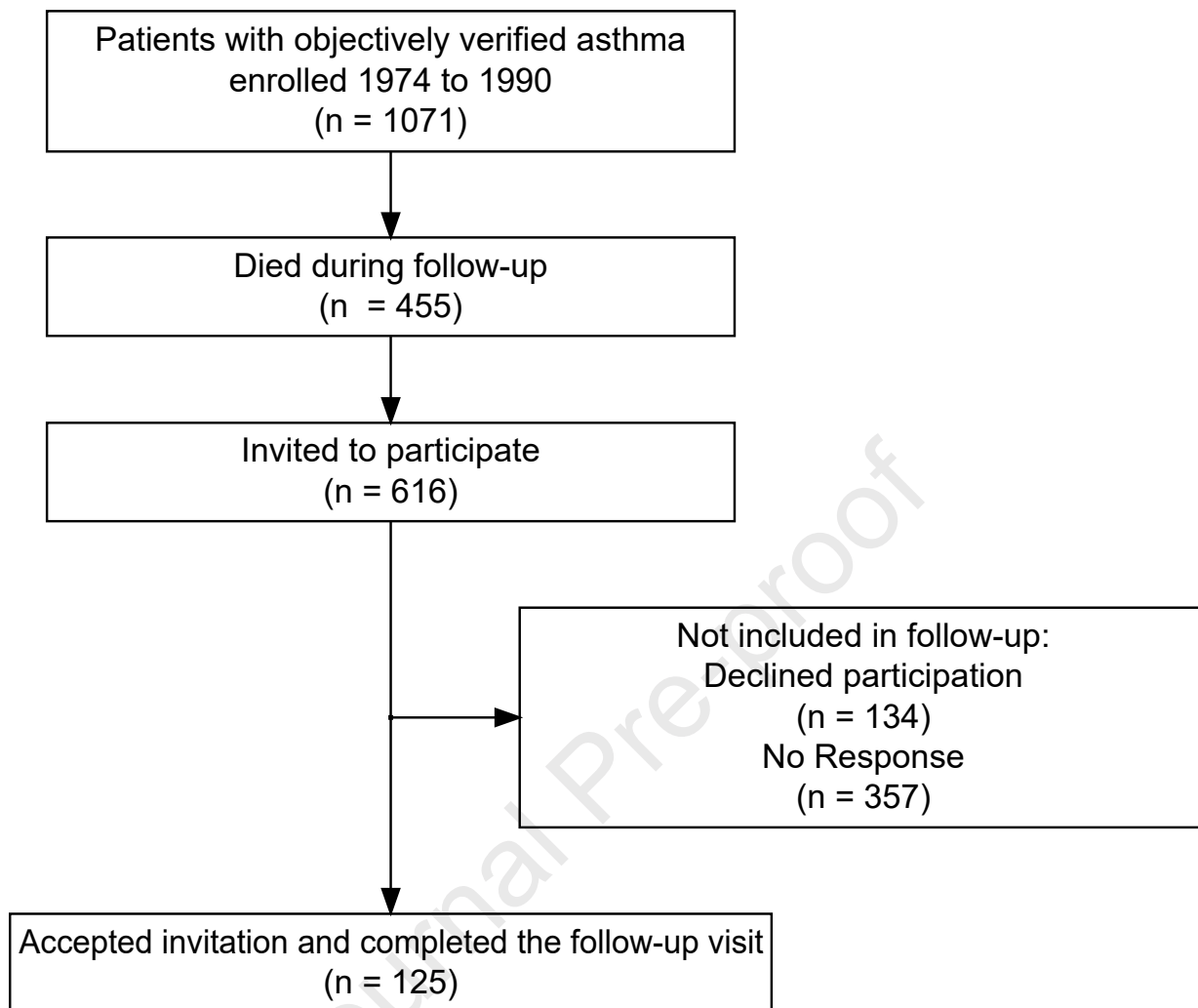
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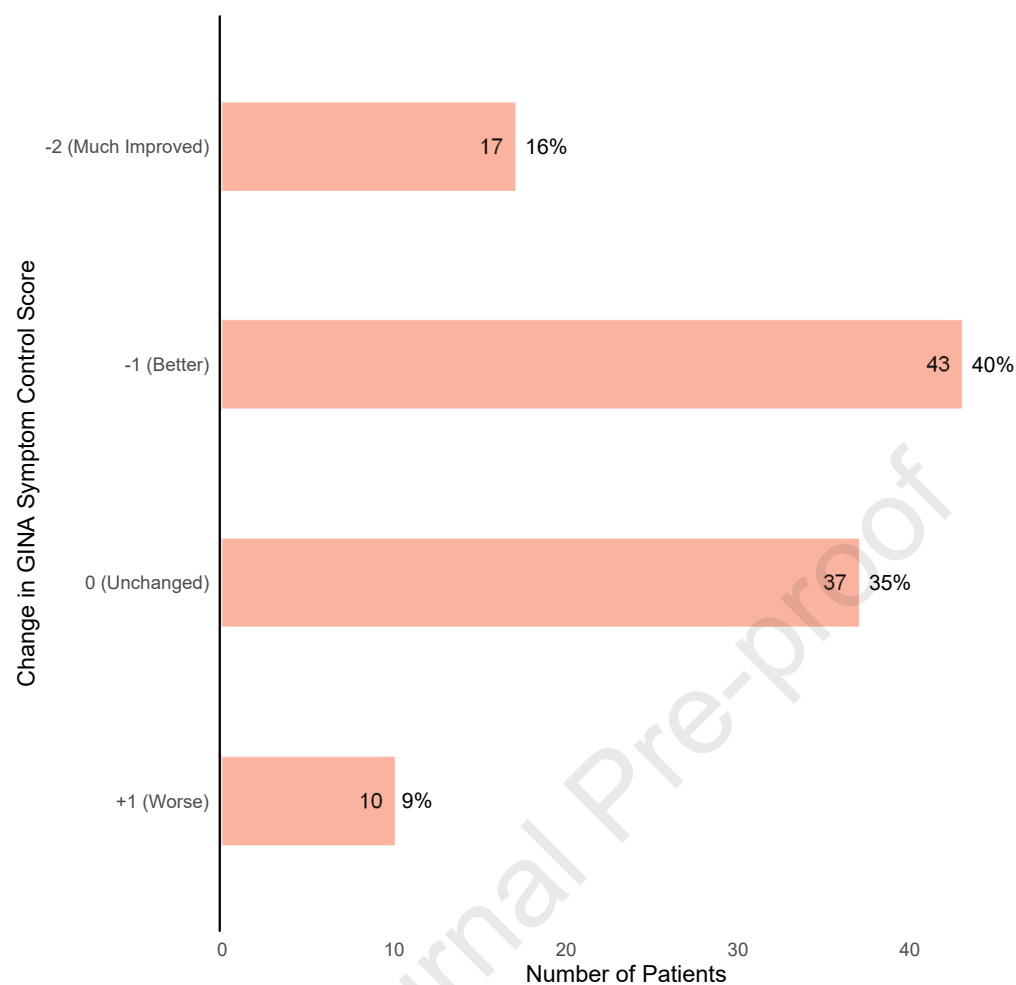
* = values derived from ANCOVA adjusted for baseline values. SD= Standard deviation. Q₁—Q₃=25th—75th percentile.

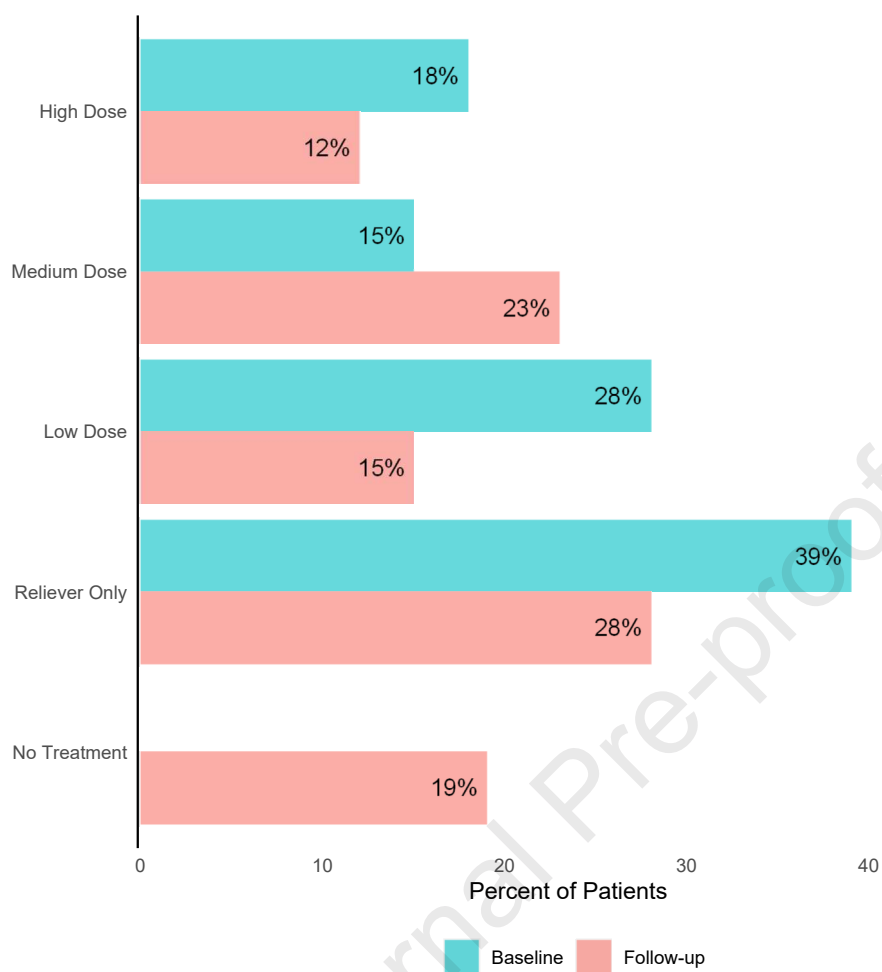
Table E3 – Baseline characteristics associated with being prescribed medium or high-dose ICS at the follow-up visit 30 years after baseline.

			Bivariate model			Multivariable model		
Baseline factors			Odds Ratio	95% CI	P-value	Odds ratio	95% CI	p-value
Age at baseline			1.00	0.95—1.05	0.860	-	-	-
Adulonset,			1.00	0.97—1.03	0.975	-	-	-
Years since symptom debut			1.00	0.95—1.05	0.975	-	-	-
GINA symptom control	Well-controlled		-	-	-	-	-	-
	Partially controlled		1.00	-	-	1.00	-	-
	Uncontrolled		0.57	0.25—1.26	0.165	0.40	0.16—1.03	0.058
Ever smoker ^a			1.39	0.58—3.33	0.467	-	-	-
Previous severe exacerbation			1.03	0.39—2.73	0.955	-	-	-
Lung Function	FEV ₁ percent predicted		0.996	0.97—1.03	0.800	-	-	-
	FEV ₁ /FVC ratio		0.97	0.92—1.02	0.259	-	-	-
Asthma test	Bronchodilator reversibility		1.02	1.00—1.05	0.11	1.02	0.99—1.05	0.208
	AHR ^b , mg/ml	<1	3.03	0.83—11.1	0.094	1.85	0.49—6.96	0.360
		≥1	1.00	-	-	1.00	-	-
	Peak flow variability		1.08	0.99—1.08	0.18	-	-	-
Asthma Medication	ICS prescribed ^c	+	3.54	1.42—8.81	0.007	3.34	1.18—9.45	0.023
	Daily β ₂ dose ^{cd} ,	>2	1.41	0.64—3.12	0.40	-	-	-
Blood Eosinophils, x 10 ⁹ /l		≥0.3	4.43	1.72—11.4	0.002	3.27	1.10—9.72	0.033
IgE total, >150 I/U			1.88	0.84—4.19	0.13	1.72	0.67—4.39	0.258
Skin prick test, negative			1.09	0.44—2.66	0.857	-	-	-

a=Current or ex-smoker. b=Airway hyperresponsiveness to histamine. c= any dose prescribed at baseline d= either doses of 100 ug salbutamol inh. or. 5 mg tbl.







Remission and changes in severity over 30 years in adults with objectively verified asthma

Oliver Djurhuus Tupper¹, Kjell Erik Julius Håkansson¹, Charlotte Suppli Ulrik^{1,2}

¹ Department of Respiratory Medicine, Copenhagen University Hospital Hvidovre, Denmark

² Institute of Clinical Medicine, University of Copenhagen, Denmark

Online Repository Text

34 **Methods**

35 *Baseline visit*

36 The patient cohort and methods used at baseline have been described previously by Ulrik et al.¹
37 The cohort of patients comprised all persons diagnosed with and followed for asthma between
38 1974-1990, at Frederiksberg Respiratory and Allergy Clinic, Denmark. Persons included were ≥ 13
39 years of age at baseline. The diagnosis of asthma was made by a specialist in respiratory medicine
40 based on a typical history (wheezing or attacks of breathlessness; chest tightness; cough triggered
41 by exercise, exposure to allergens or irritants or respiratory infections) and at least one of the
42 following: 1) FEV₁ reversibility $> 15\%$ (and an absolute increase of > 150 ml) after a standard dose
43 of β_2 -agonist, oral corticosteroid or both (30 mg/d) for 14 days.² 2) Diurnal variability in peak
44 expiratory flow (PEF) rate $> 20\%$ and absolute variation > 100 L/min.^{3,4} 3) Positive histamine
45 bronchial challenge test, as previously described by Dirksen⁵, a positive response was defined as a
46 PC₂₀ ≤ 8 mg/ml.

47 At the time of referral to the respiratory outpatient clinic, a comprehensive history was obtained:
48 known allergies; allergic symptoms; disposition to allergic disease; frequency and duration of
49 respiratory symptoms; trigger factors; type and usage of asthma medication; and the number of
50 emergency department visits and hospital admissions due to asthma worsening/exacerbation,
51 henceforth defined as severe exacerbations.

52 At the first clinic visit, the last 3 months symptoms were graded as: Grade 1 on average once a
53 week; Grade 2 more than once a week; Grade 3 daily; and; Grade 4 daily and nightly.

54 Smoking history was taken, and persons were classified as current smokers (CS), ex-smokers (ES),
55 and life-long non-smokers (NS). If a person was classified as either CS or ES pack-years were
56 calculated.

57 Total serum IgE was determined by paper radioimmunosorbent test (PRIST) (Pharmacia).⁵ The
58 following allergens were tested by standard skin prick test: birch, grass, mugwort, horse, dog, cat,
59 house dust mites (*D. pteronyssinus* and *D. farina*) and moulds (*A. iridis* and *C. herbarum*). The test
60 was considered positive if one of the allergen weals was at least the same size as the histamine
61 weal.⁵ The blood eosinophil count was determined three times for each patient; the most
62 abnormal result was recorded.⁵

63 Forced expiratory volume in one second (FEV₁), PEF and forced vital capacity (FVC) were measured
64 using a dry-wedge bellows spirometer (Vitalograph). The best of three technically acceptable
65 readings were recorded. The tests were repeated 15 minutes after inhalation of a standard dose of
66 bronchodilator. Reversibility of FEV₁ was calculated as (FEV₁ after – FEV₁ before)/FEV₁ before).

67 All baseline data were gathered from patient records. All persons went through the same
68 diagnostic algorithm for persons referred for suspected asthma.

69 *Follow-up visit*

70 The study consisted of a one-day subject program lasting approximately 3-4 hours. The following
71 investigations were carried out:

72 1) Questionnaires

73 a) Questions regarding current symptom status and inhaler medication.

74 i) Time of asthma diagnosis.

ii) Current inhaler medication – (SABA, SAMA, SABA/SAMA, low, medium or high dose ICS, LABA, LAMA, Leukotriene receptor antagonist, Theophylline, Oral corticosteroids and Biological treatment.) This was based on current prescribed medication in the Danish electronic prescription database (FMK-online) and adjusted according to what the participants did or did not take.

iii) When did you last take asthma medication – (1-60 days, 2-6 months, 6-12 months or >12 months)

iv) When did you last have asthma symptoms (wheeze, dyspnoea, chest tightness, cough and/or sputum) - (1-60 days, 2-6 months, 6-12 months or >12 months)

2) Skin prick test

a) Skin prick test was carried out according to the method described by Bousquet et al. with 12 local standard aeroallergens (Soluprick, ALK-Abelló). A different single use lancet will be used to perforate the skin through each allergen extract, after wiping the skin with alcohol with little pressure. The test will be read after 15 minutes. A wheal ≥ 3 mm is considered positive.

3) Spirometry

a) Measurements of FEV1, FVC and calculation of FEV1/FVC ratio (Vitalograph 6800 pneumotrac), according to ERS/ATS guidelines.

b) Bronchodilator reversibility test was performed 15 minutes after administration of 0.4 mg of salbutamol. A positive reversibility test was defined as an improvement of 12% and ≥ 200 ml in FEV1 from the pre-test value.

4) Fractional exhaled nitric oxide (FENO) measurement.

a) Fractional exhaled nitric oxide (FENO) was measured with EcoMedics CLD 88sp analyzer and DENOX 88 at a controlled flow rate of 50 ml/s according to American Thoracic Society (ATS) guidelines. The mean value of two measurements in parts per billion (ppb) was recorded.

5) Bronchial challenge test

a) For mannitol bronchial provocation we used a commercially available standardised test kit (Osmohale© Pharmaxis Ltd). This kit includes filled capsules of mannitol in incrementally increasing doses and a handheld dry powder inhaler. The first capsule inhaled did not contain mannitol, from the second dose mannitol was increased stepwise (5, 10, 20, 40, 80, 160, 160 and 160 mg). The participant was asked to exhale fully before a deep inhalation from the inhaler, held their breath for at least 5 seconds and then exhaled. FEV1 was be measured one minute after each dose of mannitol. The test was positive and stopped if FEV1 fell ≥ 15 % from baseline or $\geq 10\%$ between two doses or after reaching a cumulated dose of 635 mg. Post-test the participants received 0,2 mg salbutamol if deemed necessary, otherwise spontaneous recovery to FEV1 $>95\%$ of baseline value was awaited.

Statistics

The percentage of missing values for PC₂₀ was 27%. In total 34 out of 125 records (27%) were incomplete. PC₂₀ was assumed to be missing at random. We used multiple imputation to create and analyse 30 multiply imputed datasets. Continuous variables were imputed using the Markov chain Monte Carlo method. Models including categorical and continuous were variables imputed using fully conditional specification. We used the default settings of the MI procedure in SAS. The parameters of substantive interest were estimated in each imputed dataset separately, and combined using Rubin's rules. For comparison, we also performed the analysis on the subset of complete cases. We obtained similar results when the analysis was restricted to the complete cases only, apart from wider confidence intervals and higher p-values.

Comparison of follow-up values between those in remission and with active asthma, was conducted by analysis of covariance adjusting for values at baseline.

The linearity of the continuous variables to the logit of the dependent variable was assessed via the Box-Tidwell procedure.⁶ A Bonferroni correction was applied using all terms in the model resulting in statistical significance being accepted when $p < .00625$. Based on this assessment, all continuous independent

124 variables were found to be linearly related to the logit of the dependent variable. Variables that were
125 significant on bivariate analyses were included in the multivariate model.

126

127 **References**

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