Original Article

Asthma Remission by Age at Diagnosis and Gender in a Population-Based Study

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What is already known about this topic? Age of asthma onset differentiates patients in many ways. Remission is common in child-onset asthma, but seemingly less common in adult-onset asthma. Risk factors of asthma persistence from childhood to adulthood are well described.

What does this article add to our knowledge? In this study, age at asthma diagnosis after 40 years was the strongest risk factor of asthma nonremission, and age at diagnosis had a higher association with nonremission than current patient age or time from diagnosis.

How does this study impact current management guidelines? Age at asthma diagnosis should be highlighted in the guidelines as a key indicator of asthma prognosis. Adequate follow-up and research resource allocation should be provided for adult-onset, especially late adult-onset asthma.

BACKGROUND: Child-onset asthma is known to remit with high probability, but remission in adult-onset asthma is seemingly less frequent. Reports of the association between remission and asthma age of onset up to late adulthood are scarce.

OBJECTIVE: To evaluate the association between asthma remission, age at diagnosis and gender, and assess risk factors of nonremission.

METHODS: In 2016, a random sample of 16,000 subjects aged 20 to 69 years from Helsinki and Western Finland were sent a FinEsS questionnaire. Physician-diagnosed asthma was categorized by age at diagnosis to early- (0-11 years), intermediate- (12-39 years), and late-diagnosed (40-69 years) asthma. Asthma remission was defined by not having had asthma symptoms and not having used asthma medication in the past 12 months.

RESULTS: Totally, 8199 (51.5%) responded, and 879 reported physician-diagnosed asthma. Remission was most common in early-diagnosed (30.2%), followed by intermediate-diagnosed (17.9%), and least common in late-diagnosed asthma (5.0%)

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Abbreviations used
BMI- Body mass index
CI- Confidence interval
COPD- Chronic obstructive pulmonary disease
OR- Odds ratio

($P < .001$), and the median times from diagnosis were 27, 18.5, and 10 years, respectively. In males, the corresponding remission rates were 36.7%, 20.0%, and 3.4%, and in females, 20.4%, 16.6%, and 5.9% (gender difference $P < .001$). In multivariable binary logistic regression analysis, significant risk factors of asthma nonremission were intermediate (odds ratio [OR] = 2.15, 95% confidence interval: 1.37-3.36) and late diagnosis (OR = 11.06, 4.82-25.37) compared with early diagnosis, chronic obstructive pulmonary disease (COPD) (OR = 5.56, 1.26-24.49), allergic rhinitis (OR = 2.28, 1.50-3.46), and family history of asthma (OR = 1.86, 1.22-2.85). Results were similar after excluding COPD. CONCLUSION: Remission was rare in adults diagnosed with asthma after age 40 years in both genders. Late-diagnosed asthma was the most significant independent risk factor for nonremission. **(J Allergy Clin Immunol Pract 2021;9:1950-9)**

Key words: *Asthma; Remission; Gender; Age of onset; Late-onset; Early-onset; Adult; Population study*

Asthma is a chronic respiratory disease with a tendency to vary over time from more to less symptomatic periods and even remission. Remission is most accurately defined as an asymptomatic period of ≥12 months according to a recent consensus report,[1] and remitted asthma could also be considered as nonactive. Remission is noted as the most desirable, though difficult, but increasingly achievable treatment goal in both children and adults due to new treatment methods in asthma.[1]

A common symptom in children connected with childhood asthma is wheezing, which diminishes in approximately 75% of cases by mid-adulthood,[2-5] and mostly already by age 12 years.[6] Remission estimates in children vary noticeably by study methods: only 20% of asthma, which was objectively confirmed in early school-age remitted by age 19 years in Swedish data.[7] Furthermore, one-third of males but only a minority of females with persistent medication-dependent asthma diagnosed by age 19 years had remitted by 24 years of age in a recent Finnish nation-wide register study.[8] Severe asthma at baseline, female gender, and allergic sensitization are most often reported predictors of persistence of childhood asthma up to adult age.[2,3,5,7,9]

In contrast to child-onset asthma, only 3% to 17% of adult-onset asthma have remitted 5 to 25 years after the diagnosis.[10-19] As well as being more frequently persistent,[9] adult-onset asthma is more often associated with faster loss of lung function and poorer disease control than child-onset asthma.[13,20,21] In adults under 50 years of age, female gender, smoking, allergic sensitization, high body mass index (BMI), and increasing age are commonly reported risk factors of nonremission or more inadequate control of asthma symptoms, without specific knowledge of asthma age of onset.[11,12,22-24] In addition, it seems that increasing age of onset would be a predisposing factor to persistence also later in adulthood.[14]

However, studies evaluating asthma remission have rarely been based on the general population or investigated remission according to age of onset. Although child- and adult-onset asthma have different characteristics,[20,25,26] adult-onset asthma is rarely divided and compared in early- and late-onset groups, even though they seem to be distinct.[27] Late-onset asthma (>40 years) has also been less studied. In addition, gender modifies asthma incidence, persistence, and severity.[7,8,22,23,28] Therefore, this study aimed to evaluate the association between age at asthma diagnosis, asthma remission, and gender, and to assess diagnosis-age specific risk factors of nonremission in an adult general population sample. We hypothesized that asthma diagnosed later in adulthood would be least often in remission, and risk factors of nonremission would differ according to age at diagnosis.

METHODS

Data acquisition and questionnaire

This study is a part of an international FinEsS (Finland, Estonia, Sweden) study. Totally, 16,000 subjects aged 20 to 69 years, 8000 from Helsinki and 8000 from South Ostrobothnia and Vaasa areas (Western Finland), were randomly selected by Statistics Finland in 10-year-age cohorts considering also gender distributions in the local populations. Subjects were sent a FinEsS respiratory questionnaire in February 2016, and in case of a nonresponse, up to 2 reminders were sent. A more detailed description of the methods has been published elsewhere.[28,29] The flowchart of data conformation is shown in Figure 1. Subjects with incomplete response to questions about smoking habits were excluded.

Definitions of key parameters

The commonly used variables in this study were defined as follows:

Physician-diagnosed asthma by the answer "yes" to the question "Have you been diagnosed by a doctor as having asthma?"

Age at asthma diagnosis "What age were you when asthma was diagnosed?"

Nonremitted asthma as physician-diagnosed asthma in combination with "yes" to at least 1 of the following questions: "Have you, during the last 12 months, had asthma symptoms (intermittent attacks or periodic breathlessness, with or without cough or wheezing/whistling in your chest)?" OR "Have you had wheezing or whistling in your chest at any time in the last 12 months?" OR "Do you currently use asthma medication (regularly or as needed)?"

Remission of asthma in ≥12 months by reporting physician-diagnosed asthma but not fulfilling criteria for nonremitted asthma.

Allergic rhinitis "Have you been diagnosed by a doctor as having allergic rhinitis caused by pollen (caused by, eg, birch, grass, mugwort)?" OR "Have you been diagnosed by a doctor as having other allergic rhinitis (caused by, eg, cat or dog)?"

Family history of asthma "Have any of your parents, brothers, or sisters now or previously had asthma?"

Area of habitat by participation to either the Helsinki or Western Finland sample.

COPD "Have you been diagnosed by a physician as having chronic bronchitis, chronic obstructive pulmonary disease (COPD), or emphysema?"

Occupational exposure "Does your working environment have now or has there previously been a lot of dusts, gases, or fumes?"

Living in rural area in childhood "Did you live on the countryside (not in a city or suburb) during your first 5 years of life?"

Living on a farm in childhood "Did you live on a farm during your first 5 years of life?"

Exercise per week "Exercise on your free time: How often do you exercise at least 30 minutes so that you are at least slightly short of breath and get sweaty?"

Diagnosis-age specific variables were defined by reporting physician-diagnosed asthma and concomitantly age at asthma diagnosis at:

0 to 11 years as *early-diagnosed asthma*,

12 to 69 years as *adult-diagnosed asthma*,

12 to 39 years as *intermediate-diagnosed asthma*, and

40 to 69 years of age as *late-diagnosed asthma*.

Remission was also evaluated in 10-year segments of diagnosis-age.

Statistical analyses

Statistical analyses were conducted with IBM SPSS Statistics version 25 (Armonk, NY). The χ^2 test was used in testing between categorical variables. In testing between dichotomous categorical and non-normally or normally distributed continuous variables, the Mann-Whitney and *t*-test were used, respectively. In testing between trichotomous categorical and non-normally or normally distributed variables, the Kruskal-Wallis test and 1-way analysis of variance were used, respectively. Normality in continuous variables was evaluated by visual inspection of distribution. A P value of $<.05$ was considered significant, and 95% confidence intervals (CIs) were reported.

Multivariable binary logistic regression was used to determine odds ratios (ORs) and CIs for asthma nonremission compared with remission, and to simultaneously adjust for potential confounding variables. Potential covariates were included in the model on the grounds of knowledge from previous studies, clinical experience, and significant association with the outcome variable. Covariates included in the final model were age at asthma diagnosis, BMI, age, gender, smoking, COPD, living in rural area in childhood, living on a farm in childhood, exercise per week, occupational exposure, allergic rhinitis, area of habitat, and family history of asthma. Relationships of continuous time-measuring variables (age, age at diagnosis, time from diagnosis) to asthma nonremission were investigated each separately by univariate binary logistic regression, to find out which of these variables had the strongest association with nonremission. The ORs were reported in 10-year segments of the time-measuring variables to clarify the result. Sensitivity analyses were conducted by excluding coexisting COPD and altering the remission definition by leaving out the criterion for asthma medication use.

RESULTS

Remission and age at diagnosis

Totally, 8199 subjects responded (51.5%). Basic responder data and characteristics of subjects with a nonresponse are reported elsewhere.[28,29] Responders with incomplete smoking data (N = 269) were excluded (Figure 1). After exclusion, 879 of 7930 subjects (11.1%) reported physician-diagnosed asthma. In 162 (18.4%) subjects, asthma was in remission, and in 19.9% if coexisting COPD was excluded. The median time from diagnosis was 19 years, and therefore the annual remission rate was 0.97/100/year. Demographics of subjects with remitted and nonremitted asthma are shown in Table I.

Age at asthma diagnosis was reported by 842 subjects with physician-diagnosed asthma. Subjects with early-diagnosed (0-11 years) asthma had the lowest BMI, and they were most often males and had most often allergic rhinitis as opposed to intermediate-diagnosed (12-39 years) and late-diagnosed (40-69 years) asthma. In contrast, subjects with late-diagnosed asthma had the highest BMI, they were mostly females, and only a third of them had allergic rhinitis (Table II). Remission was most common in early-diagnosed (30.2%), followed by intermediate-diagnosed (17.9%), and least common in late-diagnosed asthma (5.0%) ($P < .001$) (Figure 2, *A*). The median time from diagnosis was 27, 18.5, and 10 years, respectively, and the corresponding remission rates were 1.12/100/year, 0.97/100/year, and 0.50/100/year. If coexisting COPD was excluded, remission rates were 30.8%, 18.8%, and 6.2%, respectively.

Remission was further assessed by dividing age at asthma diagnosis into 10-year groups (Figure 2, *B*). A decrease in the proportion of remitted subjects was seen by increasing age at diagnosis: 22% to 29% of subjects with asthma diagnosed at 0 to 29 years of age were in remission, but if diagnosed at age 30 to 69 years, only 4% to 8% were in remission. When remission was further assessed in 10-year groups by current age, subjects aged 30 to 39 years had the highest (28.5%) and those aged 60 to 69 years had the lowest (12.1%) proportion of remission (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org).

Risk factors of asthma nonremission

Adult-diagnosed (12-69 years) asthma (OR = 2.97, CI: 2.06-4.27) and both intermediate-diagnosed (12-39 years) (OR = 1.99, 1.35-2.92) and late-diagnosed (40-69 years) asthma (OR = 8.19, 4.31-15.55) (all $P < .001$) were significant risk factors of nonremission in relation to early-diagnosed asthma in a univariate binary logistic regression analysis. In addition, in 3 different univariate binary logistic regression analyses, the risk of nonremission was most strongly increased by age at asthma diagnosis (OR = 1.45, $P < .001$, per 10-year increase) compared with current age (OR = 1.20, $P = .001$, per 10-year increase) or time from diagnosis (OR = 1.33, $P < .001$, per 10-year decrease).

To further investigate the risk factors of asthma nonremission, we used multivariable binary logistic regression analysis, in which statistically significant risk factors of nonremitted asthma were intermediate or late diagnosis, coexisting COPD, allergic rhinitis, and family history of asthma. Female sex and current smoking showed tendency to increase risk of nonremission, and age, occupational exposure, living in a rural area in childhood, living on a farm in childhood, BMI, area of habitat, and exercise by week were not significantly associated with nonremission (Table III).

Independently analyzed, significant risk factors of nonremission in subjects with early-diagnosed asthma (0-11 years) were female gender and allergic rhinitis, and in adult-diagnosed asthma (12-69 years), family history of asthma, late-diagnosed asthma, and exercise ≥2 to 3 times per week, whereas coexisting COPD showed a high effect size (OR = 7.34) but was slightly insignificant ($P = .055$) probably due to insufficient data in the subgroup (Table III). Furthermore, if the medication usage criterion was left out of the definition of nonremission, and the

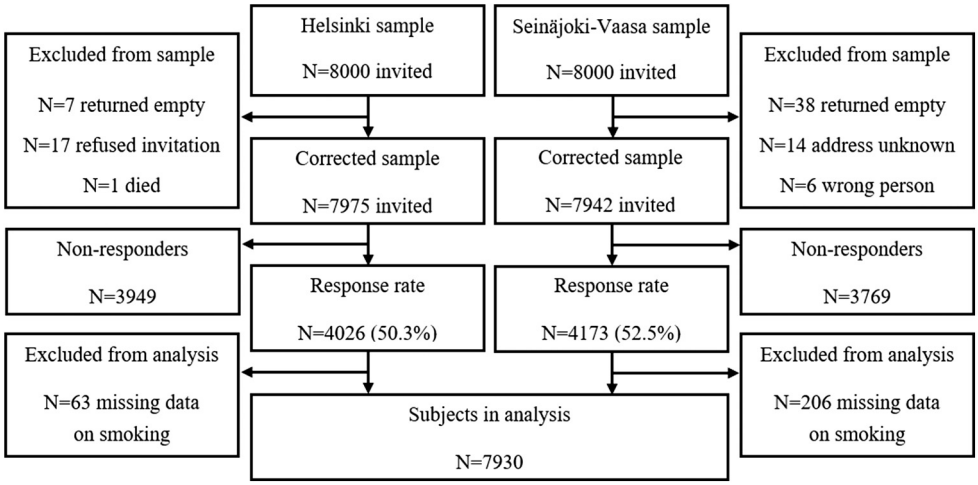

FIGURE 1. Flowchart of the study.

TABLE I. Demographics of subjects with physician-diagnosed asthma and comparison of remitted and nonremitted asthma

	Physician-diagnosed asthma (N = 879)		Remitted asthma (N = 162)		Nonremitted asthma (N = 717)		
Variable	**Median**	**Q_1-Q_3**	**Median**	**Q_1-Q_3**	**Median**	**Q_1-Q_3**	***P*#**
Age (y)	47	32-61	39	31-56	49	33-61	**.001**
Age at diagnosis (y)*	23	10-40	12	6-22	28	12-43	**<.001**
Time from diagnosis (y)*	19	10-28	23	17-23	18	8-26	**<.001**
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
BMI†	26.7	5.3	26.2	4.6	26.9	5.4	.15
	N	**%**	**N**	**%**	**N**	**%**	
Female	498	56.7	72	44.4	426	59.4	**.001**
Family history of asthma	392	44.6	54	33.3	78	10.9	**.001**
Coexisting COPD	81	9.2	3	1.9	78	10.9	**<.001**
Smoking							.16
Never	409	46.5	29	17.9	179	25.0	
Current	208	23.7	53	32.7	209	29.1	
Ex	262	29.8	80	49.4	329	45.9	
Age at diagnosis (y)*							**<.001**
0-11	245	29.1	74	49.3	171	24.7	
12-39	358	42.5	64	42.7	294	42.5	
40-69	239	28.4	12	8.0	227	32.8	
Allergic rhinitis	508	57.8	84	51.9	424	59.1	.09
Living in rural area in childhood‡	406	46.7	67	41.4	339	47.9	.13
Living on a farm in childhood§	233	27.0	36	22.2	197	28.1	.13
Exercise ≥2-3 times per week‖	594	69.5	102	65.0	492	70.5	.16
Occupational exposure¶	335	39.3	49	31.0	286	41.2	**.018**
Helsinki as habitat	434	49.4	82	50.6	352	49.1	.73

BMI, Body mass index; *COPD*, chronic obstructive pulmonary disease; Q_1-Q_3, quartiles; *SD*, standard deviation.
Bolded text indicates statistical significance ($P < .05$).
Missing data: *37, †13, ‡10, §15, ‖24, ¶27.
#Measured by the χ^2 test in categorical variables, by the Mann-Whitney test in non-normally distributed continuous variables, and by the *t*-test in BMI.

definition was solely based on symptoms, exercise was no more a risk factor of nonremission, whereas other significant associations remained (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

A similar regression analysis was also conducted separately for intermediate- (12-39 years) and late-diagnosed (40-69 years) asthma. The only significant risk factor of nonremission in intermediate-diagnosed asthma (N = 328 in regression) was

TABLE II. Demographics and comparison of subjects with physician-diagnosed asthma categorized by age at asthma diagnosis

	Early-diagnosed asthma (0-11 y) (N = 245)		Intermediate-diagnosed asthma (12-39 y) (N = 358)		Late-diagnosed asthma (40-69 years) (N = 239)		
Variable	**Median**	**Q_1-Q_3**	**Median**	**Q_1-Q_3**	**Median**	**Q_1-Q_3**	***P*#**
Age (y)	32	26-44	42	32-54	62	57-66	**<.001**
Time from diagnosis (y)*	27	20-39	19	10-28	10	4-17	**<.001**
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
BMI†	25.6	4.8	26.5	5.2	28.1	5.4	**<.001**
	N	**%**	**N**	**%**	**N**	**%**	
Female	98	40.0	223	62.3	152	63.6	**<.001**
Family history of asthma	112	45.7	159	44.4	104	43.5	.89
Coexisting COPD	8	3.3	28	7.8	44	18.4	**<.001**
Smoking							**.002**
Never	124	50.6	172	48.0	98	41.0	
Current	68	27.8	80	22.3	49	20.5	
Ex	53	21.6	106	29.6	92	38.5	
Allergic rhinitis	174	71.0	228	63.7	85	35.6	**<.001**
Living in rural area in childhood‡	99	40.4	155	43.8	139	59.7	**<.001**
Living on a farm in childhood§	43	17.6	75	21.3	108	46.8	**<.001**
Exercise ≥2-3 times per week‖	165	67.9	248	71.5	160	69.6	.64
Occupational exposure¶	76	31.5	125	36.1	117	51.3	**<.001**
Helsinki as habitat	131	53.5	184	51.4	100	41.8	**.022**

BMI, Body mass index; *COPD*, chronic obstructive pulmonary disease; *Q_1-Q_3*, quartiles; *SD*, standard deviation.
Bolded text indicates statistical significance ($P < .05$).
Missing data: *37, †13, ‡10, §15, ‖24, ¶27.
#Measured by the χ^2 test in categorical variables, by the Kruskal-Wallis test in non-normally distributed continuous variables, and by 1-way analysis of variance in BMI.

exercise ≥2 to 3 times per week (OR = 2.29, 1.19-4.38, P = .013). Because the number of subjects in remission was very low in late-diagnosed asthma, risk factors of nonremission could not be reliably assessed. However, all the subjects who had coexisting COPD were not in remission.

As subjects with coexisting COPD were excluded to investigate its possible confounding effect, current smoking (OR = 1.84, 1.05-3.23, P = .033) became an additional significant risk factor of nonremission in physician-diagnosed asthma in similar regression analysis as in Table III (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). The results remained mainly similar also regarding risk factors of adult-diagnosed asthma nonremission. In addition, if time from diagnosis was included as an additional covariate to the regression model, the association with late-diagnosed asthma remained statistically significant (Table E3, available in this article's Online Repository at www.jaci-inpractice.org).

Remission and gender

Based on previous knowledge of gender differences in asthma and a significant association between gender and asthma remission in this study, gender-specific remission was assessed. Of males, 23.6%, and of females, 14.5% were in remission (P = .001). Males and females in remission versus nonremission had lower age at asthma diagnosis, less often coexisting COPD and occupational exposure. Furthermore, males in remission versus nonremission were younger and had less often a family history of asthma (Table IV).

Males with early-diagnosed asthma were more frequently in remission than females ($P < .006$), but no significant difference was found in remission of intermediate- or late-diagnosed asthma between genders (Figure 3, *A*). Furthermore, when investigated in 10-year groups, a trend of decreasing remission by increasing diagnosis-age was seen in both genders (Figure 3, *B*). As diagnosed at 0 to 29 years of age, asthma was in remission in 27% to 35% and 20% to 23% of males and females, respectively. In contrast, if diagnosis was made in 30 to 69 years of age, corresponding percentages were 0% to 12% and 5% to 7%.

DISCUSSION

The primary result of this study was that remission of asthma became rarer as the age at diagnosis of asthma increased. The finding remained similar after adjusting by multiple confounding variables. Furthermore, age at diagnosis pooled in 10-year groups showed that any asthma diagnosed after age 30 years was prone not to be in remission in both genders.

The annual remission rate was 0.97/100/year in all subjects with physician-diagnosed asthma, 1.12/100/year in early-diagnosed, 0.97/100/year in intermediate-diagnosed, and 0.50/100/year in late-diagnosed asthma. The overall annual remission rate was similar to earlier reports,[11,17] but diagnosis-age centered remission rates have not been assessed previously, to the best of our knowledge. The cut-points of the diagnosis-age groups were chosen mainly based on asthma incidence switches[28] and cut-points used in the existing literature.[25] Particularly, age 40 years as a cut-point for adult-onset asthma has also been

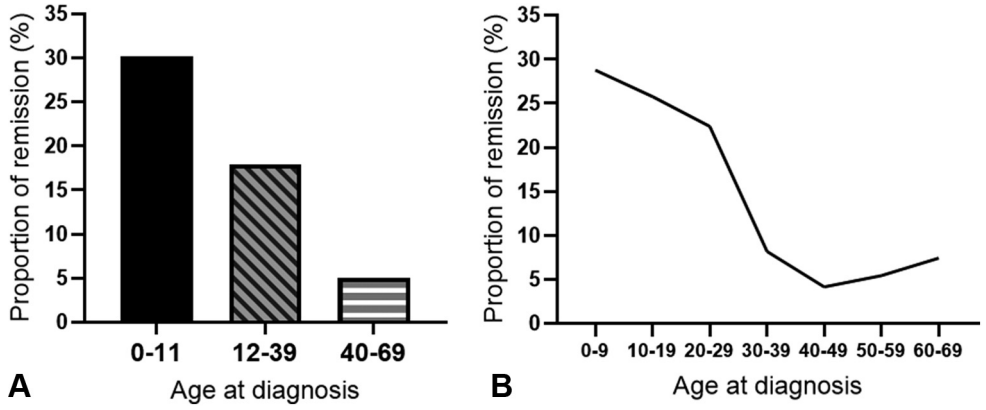

FIGURE 2. Remission (%) in subjects with physician-diagnosed asthma in groups defined by age at asthma diagnosis. In (**A**) is shown the proportion of remission in subjects with early (0-11), intermediate (12-39 years) and late-diagnosed (40-69 years) asthma. In (**B**) is shown the proportion of remission in subjects divided into 10-year groups by age at asthma diagnosis.

TABLE III. Risk factors of asthma nonremission compared with remission in subjects with physician-diagnosed asthma, and separately in subjects with early-diagnosed (0-11 years) and adult-diagnosed (12-69 years) asthma in multivariable binary logistic regression analysis*

	Physician-diagnosed asthma (N = 773)		Early-diagnosed asthma (0-11 y) (N = 234)		Adult-diagnosed asthma (12-69 y) (N = 539)	
Variable	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Female	1.47 (0.96-2.25)	.07	**2.39 (1.17-4.87)**	**.017**	1.07 (0.60-1.90)	.82
Family history of asthma	**1.86 (1.22-2.85)**	**.004**	1.77 (0.89-3.51)	.10	**1.78 (1.00-3.16)**	**.050**
Smoking						
Never	1		1		1	
Current	1.66 (0.96-2.87)	.068	1.48 (0.66-3.36)	.34	1.94 (0.85-4.43)	.11
Ex	0.99 (0.61-1.60)	.97	0.93 (0.40-2.14)	.86	1.19 (0.64-2.19)	.58
Occupational exposure	1.30 (0.83-2.04)	.26	1.43 (0.68-2.98)	.35	1.30 (0.71-2.38)	.39
Living in rural area in childhood	1.19 (0.69-2.05)	.52	1.46 (0.60-3.56)	.41	0.91 (0.44-1.87)	.79
Living on a farm in childhood	0.80 (0.44-1.46)	.47	0.85 (0.29-2.50)	.77	0.83 (0.39-1.78)	.64
BMI						
<24.99	1		1		1	
25-29.99	1.00 (0.62-1.60)	.99	0.84 (0.39-1.82)	.66	1.07 (0.57-2.03)	.83
30-34.99	0.92 (0.52-1.63)	.77	0.85 (0.34-2.15)	.74	0.92 (0.42-1.98)	.82
>35	1.84 (0.58-5.87)	.30	1.42 (0.18-11.48)	.74	2.30 (0.49-10.68)	.29
Age at diagnosis (y)			N/D			
0-11	1					
12-39	**2.15 (1.37-3.37)**	**.001**			1	
40-69	**11.08 (4.82-25.45)**	**<.001**			**5.04 (2.17-11.71)**	**<.001**
Exercise ≥2-3 times per week	1.34 (0.87-2.07)	.18	0.64 (0.31-1.30)	.22	**2.16 (1.20-3.87)**	**.010**
Allergic rhinitis	**2.29 (1.50-3.47)**	**<.001**	**4.89 (2.44-9.80)**	**<.001**	1.58 (0.89-2.80)	.12
Age (y)						
60-69	1		1		1	
50-59	1.40 (0.66-2.97)	.38	0.58 (0.13-2.59)	.48	1.86 (0.74-4.72)	.19
40-49	1.11 (0.54-2.31)	.78	0.81 (0.19-3.53)	.78	1.03 (0.42-2.48)	.96
30-39	0.97 (0.48-1.96)	.94	0.40 (0.11-1.49)	.17	1.34 (0.54-3.29)	.53
20-29	1.58 (0.75-3.31)	.23	0.78 (0.22-2.82)	.71	1.81 (0.63-5.17)	.27
Coexisting COPD	**5.56 (1.26-24.51)**	**.023**	1.66 (0.15-17.85)	.68	7.34 (0.96-56.19)	.055
Helsinki as habitat	0.98 (0.62-1.55)	.92	1.01 (0.48-2.15)	.97	0.99 (0.54-1.83)	.98

BMI, Body mass index; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *OR*, odds ratio.
Bolded text indicates statistical significance ($P < .05$).
*Three different multiple logistic regression analyses were conducted with a target variable of remission of asthma. Nonremission was coded as 1 and remission as 0. Reported ORs have been adjusted for all the variables listed.

TABLE IV. Demographics of male and female subjects with physician-diagnosed asthma and comparison of gender-specific remitted and nonremitted asthma

	Males				Females			
	Physician-diagnosed asthma (N = 381)	Remitted asthma (N = 90)	Nonremitted asthma (N = 291)		Physician-diagnosed asthma (N = 498)	Remitted asthma (N = 72)	Nonremitted asthma (N = 426)	
Variable	Median (Q_1-Q_3)	Median (Q_1-Q_3)	Median (Q_1-Q_3)	$P^{\#}$	Median (Q_1-Q_3)	Median (Q_1-Q_3)	Median (Q_1-Q_3)	$P^{\#}$
Age (y)	44 (32-59)	36 (29-52)	46 (33-60)	**.004**	49 (33-61)	45 (32-59)	51 (33-62)	.09
Age at diagnosis (y)*	18 (6-35)	9 (5-19)	21 (8-40)	**<.001**	28 (14-43)	17 (10-25)	30 (15-45)	**<.001**
Time from diagnosis (y)*	20 (11-29)	24 (18-27)	18 (10-27)	**<.001**	18 (8-27)	23 (15-33)	17 (7-26)	**.001**
	Mean (SD)	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	Mean (SD)	
BMI[†]	27.1 (5.0)	26.6 (4.8)	27.2 (5.0)	.37	26.5 (5.5)	25.6 (4.4)	26.7 (5.6)	.15
	N (%)	N (%)	N (%)		N (%)	N (%)	N (%)	
Family history of asthma	154 (40.4)	25 (27.8)	129 (44.3)	**.005**	238 (47.8)	29 (40.3)	209 (49.1)	.17
Coexisting COPD	42 (11.0)	2 (2.2)	40 (13.7)	**.002**	39 (7.8)	1 (1.4)	38 (8.9)	**.028**
Smoking				.36				.21
Never	147 (38.6)	38 (42.2)	109 (37.5)		262 (52.6)	42 (58.3)	220 (51.6)	
Current	107 (28.1)	20 (22.2)	87 (29.9)		101 (20.3)	9 (12.5)	92 (21.6)	
Ex	127 (33.3)	32 (35.6)	95 (32.6)		135 (27.1)	21 (29.2)	114 (26.8)	
Age at diagnosis (y)*				**<.001**				**.002**
0-11	147 (39.8)	54 (64.3)	93 (32.6)		98 (20.7)	20 (30.3)	78 (19.2)	
12-39	135 (36.6)	27 (32.1)	108 (37.9)		223 (47.1)	37 (56.1)	186 (45.7)	
40-69	87 (23.6)	3 (3.6)	84 (29.5)		152 (32.1)	9 (13.6)	143 (35.1)	
Allergic rhinitis	219 (57.5)	48 (53.3)	171 (58.8)	.36	289 (58.0)	36 (50.0)	253 (59.4)	.14
Living in rural area in childhood[‡]	168 (44.7)	36 (40.0)	132 (46.2)	.31	238 (48.3)	31 (43.1)	207 (49.2)	.34
Living on a farm in childhood[§]	100 (26.6)	21 (23.3)	79 (27.6)	.42	133 (27.3)	15 (20.8)	118 (28.4)	.19
Exercise ≥2-3 times per week[‖]	236 (63.6)	54 (60.7)	182 (64.5)	.51	358 (74.0)	48 (70.6)	310 (74.5)	.49
Occupational exposure[¶]	190 (51.5)	36 (41.4)	154 (54.6)	**.031**	145 (30.0)	13 (18.3)	132 (32.0)	**.020**
Helsinki as habitat	189 (49.6)	43 (47.8)	146 (50.2)	.69	245 (49.2)	39 (54.2)	206 (48.4)	.36

BMI, Body mass index; *COPD*, chronic obstructive pulmonary disease; Q_1-Q_3, quartiles; *SD*, standard deviation.

Bolded text indicates statistical significance ($P < .05$).

Missing in males: *12, [†]3, [‡]5, [§]5, [‖]10, [¶]12. Missing in females: *25, [†]10, [‡]5, [§]10, [‖]14, [¶]15.

#Measured by the χ^2 test in categorical variables, by the Mann-Whitney test in non-normally distributed continuous variables, and by the *t*-test in BMI.

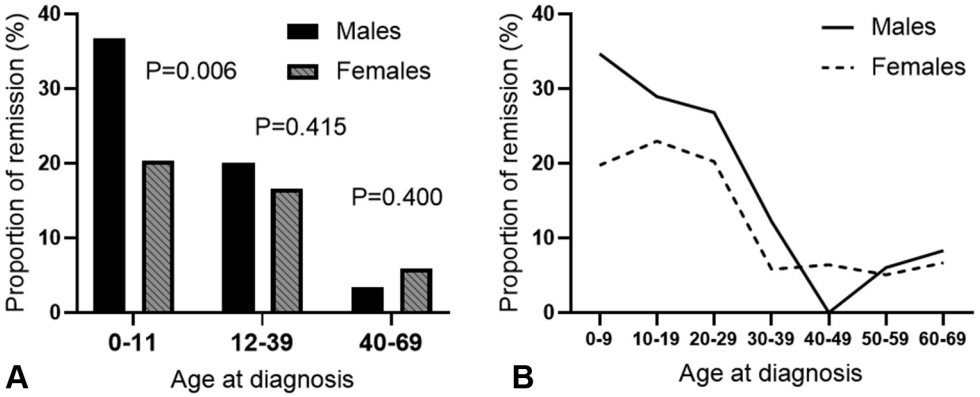

FIGURE 3. Gender-specific remission (%) in subjects with physician-diagnosed asthma in groups defined by age at asthma diagnosis. In (**A**) is shown the proportion of remission in subjects with early (0-11), intermediate (12-39 years) and late-diagnosed (40-69 years) asthma. In (**B**) is shown the proportion of remission in subjects divided into 10-year groups by age at asthma diagnosis.

previously proposed.[27] The remission definition we used adapted to a recent consensus report that argued ≥12 months to be the most optimal asymptomatic time frame to the definition of asthma remission.[1]

Early-diagnosed asthma (<12 years) was in remission in 30% of subjects: in 37% of males and 20% of females. Child-onset asthma is mostly defined similarly, as beginning at <12 years of age in other studies comparing asthma by age of onset.[25] Our remission estimates were low compared with studies with a symptom-based definition of asthma,[3] but very similar to studies that have included only physician-diagnosed or objectively confirmed asthma.[7,8] In addition, we found 2 risk factors of nonremission in early-diagnosed asthma: allergic rhinitis and female gender, similarly as in earlier reports.[3,7,9]

Intermediate-diagnosed asthma (12-39 years) was in remission in 17.9% of subjects, which settles between earlier findings.[11,30] The diagnosis-age definition in this group reflects quite well those of adult-onset or late-onset asthma in previous studies comparing asthma by age of onset because older subjects have been left out in most of them.[25,30] Interestingly, exercise ≥2 to 3 times per week was the only significant risk factor of nonremission in this group, which however lost its significance if subjects reporting current asthma medication use but not symptoms were considered as remitted. This suggests preventative medication usage in exercising subjects to explain the result. Other studies have similarly found only few risk factors of nonremission in subjects with similar diagnosis age: nasal polyps, allergic sensitization, worse lung function at baseline, inhaled corticosteroid use.[10,11,17,30] Daily physical activity has also been found to decelerate the loss of lung function in the long term in adult-onset asthma.[31]

Only 5% of subjects with late-diagnosed asthma were currently in remission. The result is in line with a previous prospective case-control study that reported remission rate by detailed diagnosis age in older age.[11] Our study was underpowered to determine risk factors of nonremitted late-diagnosed asthma, but all the subjects who had coexisting COPD were not in remission. Furthermore, remission was rarest in subjects aged 60 to 69 years, which could result from a higher proportion of worse-prognostic adult-diagnosed asthma in those with older age, but also from an increase in other comorbid conditions associated with age, which may play a role in asthma control.[32,33] Comorbid COPD is reportedly a predisposing factor to poorer lung function in asthma,[34,35] but other comorbidities are also found to be more prevalent in patients with coexisting asthma and COPD than other patients with asthma.[34] Nevertheless, to the best of our knowledge, this was the first study to investigate risk factors of asthma nonremission by detailed asthma age of onset in adulthood and one of the few studies to investigate remission of asthma in the elderly population.

The 2 most remarkable independent risk factors of asthma nonremission were late-diagnosed asthma (OR = 11.1) and coexisting COPD (OR = 5.6). Exclusion of coexisting COPD did not affect the effect size or significance of late diagnosis (40-69 years) as a risk factor for nonremission, supporting its role as a real-life independent risk factor. Support for late diagnosis as a COPD-independent risk factor for poorer asthma prognosis is also provided in another study.[35] However, the effect size of late diagnosis age as a risk factor of asthma nonremission in an extensive stratified regression model has not been described earlier, to the best of our knowledge.

Current smoking transformed into a significant risk factor of asthma nonremission as subjects with coexisting COPD were excluded. Current smoking and smoking history are both indeed found to increase the risk of at least more difficult asthma.[36,37] Furthermore, BMI was not a significant risk factor of nonremission in any diagnosis-age group. High BMI was previously found to increase risk of more difficult asthma in a "dose-response" manner,[38] but another study, which also found an association between high BMI and more difficult asthma, showed that BMI and the actual remission of asthma were not associated,[11] consistent with this study.

In general, retrospective studies have limitations. Underreporting mild asthma due to recall bias is found to be common[39] as well as misdiagnosis of asthma.[40] However, in Finland, the standard practice is to confirm asthma and COPD diagnoses with objective lung function tests highly recommended by Global Initiative for Asthma and the Finnish national health care guidelines, increasing the reliability of asthma diagnoses.[41,42] In addition, all citizens in Finland are covered by the National Health Insurance scheme and issued a personal health insurance card. This card is replaced usually 6 to 8 months from asthma diagnosis, containing not only asthma medication reimbursement information but also the replacement date. The card is

frequently used as medication is purchased. Thus, a considerable proportion of the respondents had verified data of their age at asthma diagnosis at hand when they filled the questionnaire. In addition, reimbursement of asthma medication[8] contributes a notable financial benefit to patients, which further enhances the memory related to precise diagnosis age, which was asked the study subjects with a well-validated questionnaire.[28]

Furthermore, in this study, a risk of misinterpretation of early-diagnosed asthma to adult-diagnosed asthma is present[43] as child-onset asthma may relapse after a long remission period in mid-adulthood.[4,5] However, subjects diagnosed in childhood are mostly allergic and males, whereas adult-diagnosed subjects mostly nonallergic and females,[20,28] therefore having different permanent characteristics. This also applied to our findings, suggesting that misinterpretation of early-onset relapsed asthma to adult-diagnosed asthma would not have caused a major bias. On the other hand, retrospective self-reported asthma age of onset assessment is previously found to be very specific.[39,44] For these reasons, we consider the reported asthma diagnoses in the present study to be precise and comprehensive, and only little misclassification of early-diagnosed asthma to late-diagnosed asthma or asthma to COPD in the older age groups. Therefore, although some mild asthma is probably left out, overall, we consider the reported asthma diagnoses in this study to be accurate.

Our data were based on an age-comprehensive cross-sectional random sample of general adult population: subjects were invited to the study with no exclusions, and all subjects who filled the questionnaire appropriately were included. In addition, the effect of nonresponse is previously discussed to be moderate in this study.[28,29] It should also be noted that cohort effect affects the results, as the oldest subjects had lived their childhood a long time ago, when asthma incidence was lower and identification more difficult. However, similar data would be very troublesome to collect prospectively. Furthermore, the data were based solely on the questionnaire, and clinical parameters were not available. Therefore, the evidence of distinguishing nonremitted and remitted asthma was not as accurate as in clinical data. However, clinical data are usually collected from secondary health care. Thus, we consider the results from these data accurate and generalizable to the primary health care patients as subjects conformed the general population.

As discussed, remission of asthma was lowest in subjects with later diagnosis age as has been reported earlier,[45] and the finding was parallel in both genders. In addition, it is shown that in adult subjects, current adult-onset asthma is more common than current child-onset asthma[8,28] and that adult-onset asthma predisposes to poorer response to traditional asthma medications, and uncontrolled asthma,[20] the mechanism being still unknown.[32,33] Taking all these findings into account, adult-onset asthma contributes a marked burden to the health care system altogether. What is also notable is that age of onset had the strongest association with asthma remission of the time-measuring variables in this study, which implicates that it would be a better factor to characterize asthma remission tendency than the age or duration of asthma of patients. In conclusion, to affect prognosis of asthma, follow-up resources should be increased in adult-onset asthma, and follow-up needs to be intensified especially in patients whose asthma has occurred after 30 years of age as they have the highest risk of nonremittance.

In conclusion, age at asthma diagnosis predicted well the probability of asthma remission through the age span. Adult-diagnosed asthma was rarely in remission, and even less often with increasing age at diagnosis. Gender did not seem to have a significant impact on remission of asthma diagnosed in adulthood. Age at diagnosis also defined the risk factors of nonremission, suggesting distinct differences between these phenotypes. More resources to adult-onset and especially late-onset adult asthma should be targeted, in terms of follow-up as well as in research, especially to unravel novel targets for more effective prevention or treatment methods.

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As similar regression analysis with a similar definition of nonremission as in Table E1 was conducted separately for intermediate- (12-39 years) and late-diagnosed (40-69 years) asthma, no significant risk factors of nonremission were found in intermediate-diagnosed (12-39 years) asthma. Because the number of subjects in remission was very low in late-diagnosed asthma, risk factors of nonremission could not be reliably assessed.

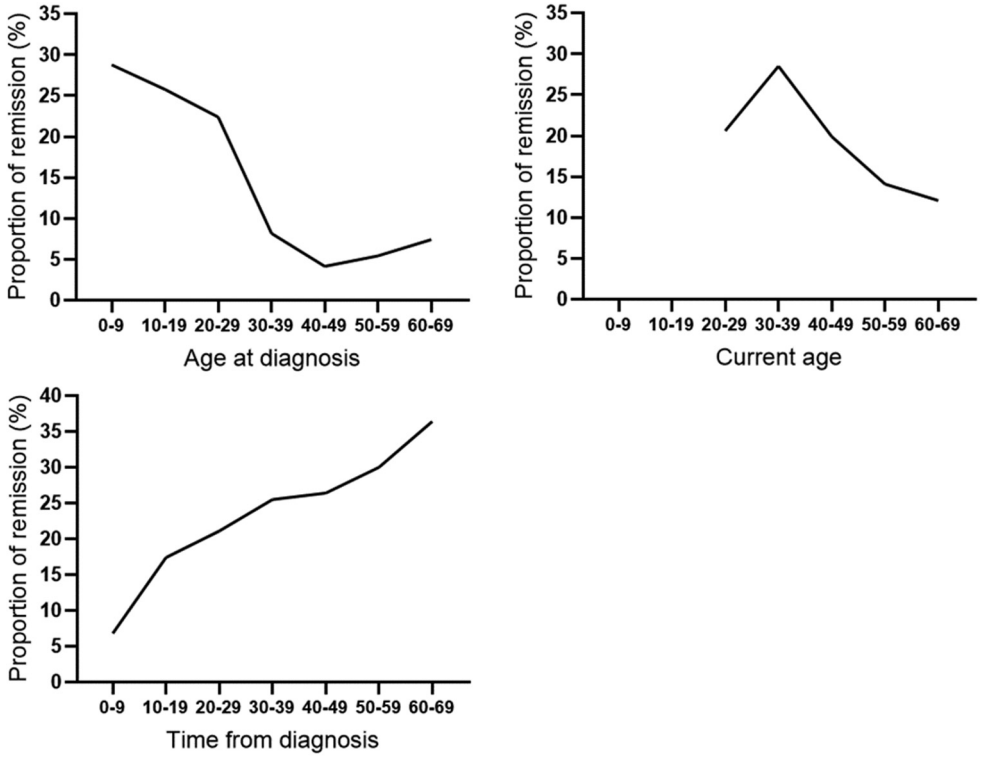

FIGURE E1. Remission (%) in subjects with physician-diagnosed asthma in relation to age at asthma diagnosis, current age, and time from diagnosis in 10-year categories.

TABLE E1. Risk factors of asthma nonremission compared with remission in subjects reporting physician-diagnosed asthma and separately in subjects with early-diagnosed (0-11 years) and adult-diagnosed (12-69 years) asthma in multivariable binary logistic regression analysis as the criterion of reporting not using asthma medication was removed from the definition of asthma remission*

	Physician-diagnosed asthma (N = 773)		Early-diagnosed asthma (0-11 y) (N = 234)		Adult-diagnosed asthma (12-69 y) (N = 539)	
Variable	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Female	1.20 (0.84-1.71)	.32	**2.01 (1.05-3.86)**	**.035**	0.94 (0.60-1.47)	.78
Family history of asthma	**1.74 (1.23-2.46)**	**.002**	1.64 (0.87-3.08)	.13	**1.69 (1.10-2.61)**	**.017**
Smoking						
Never	1		1		1	
Current	1.36 (0.86-2.13)	.19	1.07 (0.51-2.25)	.87	1.52 (0.82-1.81)	.18
Ex	0.87 (0.59-1.30)	.50	0.93 (0.42-2.05)	.86	0.87 (0.54-1.39)	.55
Occupational exposure	**1.46 (1.01-2.12)**	**.046**	1.83 (0.92-3.67)	.09	1.38 (0.88-2.18)	.16
Living in rural area in childhood	1.28 (0.82-2.00)	.28	1.42 (0.63-3.21)	.39	1.19 (0.68-2.08)	.55
Living on a farm in childhood	0.90 (0.55-1.48)	.68	0.85 (0.32-2.27)	.74	0.96 (0.52-1.75)	.88
BMI						
<24.99	1		1		1	
25-29.99	1.26 (0.85-1.87)	.25	1.11 (0.54-2.29)	.78	1.32 (0.81-2.13)	.27
30-34.99	1.44 (0.88-2.37)	.15	0.94 (0.40-2.21)	.88	1.72 (0.91-3.25)	.10
>35	2.32 (0.96-5.59)	.062	2.17 (0.30-15.89)	.45	2.63 (0.95-7.30)	.064
Age at diagnosis (y)			N/D			
0-11	1					
12-39	**1.63 (1.09-2.43)**	**.017**			1	
40-69	**3.41 (1.85-6.27)**	**<.001**			**2.06 (1.15-3.69)**	**.016**
Exercise ≥2-3 times per week	1.02 (0.71-1.49)	.91	0.56 (0.29-1.09)	.09	1.34 (0.84-2.15)	.22
Allergic rhinitis	**1.69 (1.19-2.42)**	**.004**	**3.50 (1.80-6.82)**	**<.001**	1.35 (0.87-2.10)	.22
Age (y)						
60-69	1		1		1	
50-59	1.36 (0.76-2.42)	.30	0.54 (0.13-2.33)	.41	1.64 (0.86-3.15)	.14
40-49	1.04 (0.57-1.89)	.91	0.45 (0.11-1.80)	.26	1.12 (0.56-2.26)	.75
30-39	0.99 (0.54-1.78)	.96	0.41 (0.12-1.46)	.17	1.12 (0.55-2.31)	.75
20-29	1.65 (0.88-3.11)	.12	0.71 (0.21-2.45)	.59	1.85 (0.79-4.37)	.16
Coexisting COPD	2.18 (0.98-4.85)	.057	2.51 (0.26-24.23)	.43	1.96 (0.83-4.63)	.12
Helsinki as habitat	1.04 (0.71-1.51)	.86	1.29 (0.64-2.59)	.48	1.00 (0.62-1.59)	.99

BMI, Body mass index; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *OR*, odds ratio.
Bolded text indicates statistical significance ($P < .05$).
*Three different multiple logistic regression analyses were conducted with a target variable of remission of asthma. Nonremission was coded as 1 and remission as 0. Reported ORs have been adjusted for all the variables listed.

TABLE E2. Risk factors of asthma nonremission compared with remission in subjects with physician-diagnosed asthma and adult-diagnosed (12-69 years) asthma in multivariable binary logistic regression analysis as coexisting COPD was excluded*

	Physician-diagnosed asthma, COPD excluded (N = 707)		Adult-diagnosed asthma (12-69 y), COPD excluded (N = 481)	
Variable	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Female	1.41 (0.92-2.16)	.12	1.02 (0.57-1.82)	.96
Family history of asthma	**1.93 (1.26-2.96)**	**.003**	1.74 (0.98-3.10)	.060
Smoking		**.033**		.07
Never	1	.95	1	.62
Current	**1.84 (1.05-3.23)**		2.20 (0.94-5.19)	
Ex	0.98 (0.61-1.59)		1.17 (0.63-2.16)	
Occupational exposure	1.20 (0.76-1.89)	.43	1.20 (0.65-2.19)	.56
Living in rural area in childhood	1.26 (0.72-2.18)	.42	0.98 (0.47-2.05)	.95
Living on a farm in childhood	0.77 (0.42-1.41)	.40	0.77 (0.36-1.67)	.51
BMI		.87		.98
<24.99	1	.61	1	.66
25-29.99	0.96 (0.60-1.55)	.35	1.01 (0.53-1.91)	.36
30-34.99	0.86 (0.48-1.53)		0.84 (0.39-1.82)	
>35	1.74 (0.54-5.62)		2.05 (0.44-9.57)	
Age at diagnosis (y)		**.001**		**<.001**
0-11	1	**<.001**		
12-39	**2.20 (1.40-3.46)**		1	
40-69	**11.48 (4.93-26.72)**		**4.87 (2.07-11.43)**	
Exercise ≥2-3 times per week	1.34 (0.86-2.07)	.19	**2.03 (1.13-3.67)**	**.019**
Allergic rhinitis	**2.34 (1.53-3.57)**	**<.001**	1.54 (0.86-2.75)	.15
Age (y)				
60-69	1		1	
50-59	1.55 (0.72-3.35)	.27	2.12 (0.81-5.56)	.13
40-49	1.12 (0.54-2.35)	.76	0.99 (0.41-2.41)	.98
30-39	0.98 (0.48-1.99)	.95	1.28 (0.52-3.17)	.60
20-29	1.68 (0.79-3.57)	.17	1.75 (0.61-5.04)	.30
Helsinki as habitat	0.96 (0.60-1.53)	.85	0.93 (0.50-1.73)	.82

BMI, Body mass index; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *OR*, odds ratio.
Bolded text indicates statistical significance ($P < .05$).
*Two different multiple logistic regression analyses were conducted with a target variable of remission of asthma. Nonremission was coded as 1 and remission as 0. Reported ORs have been adjusted for all the variables listed.

TABLE E3. Risk factors of asthma nonremission compared with remission in subjects with physician-diagnosed asthma in multivariable binary logistic regression analysis as time from diagnosis variable was included, and in addition as coexisting COPD was excluded*

	Physician-diagnosed asthma (N = 773)		Physician-diagnosed asthma, COPD excluded (N = 707)	
Variable	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Female	1.47 (0.96-2.24)	.077	1.41 (0.92-2.16)	.12
Family history of asthma	**1.88 (1.23-2.87)**	**.004**	**1.95 (1.27-3.00)**	**.002**
Smoking				
Never	1		1	
Current	1.68 (0.97-2.90)	.066	**1.85 (1.05-3.26)**	**.033**
Ex	0.99 (0.62-1.61)	.98	0.99 (0.61-1.60)	.95
Occupational exposure	1.28 (0.81-2.01)	.29	1.18 (0.75-1.87)	.47
Living in rural area in childhood	1.17 (0.68-2.02)	.57	1.23 (0.71-2.15)	.46
Living on a farm in childhood	0.80 (0.44-1.45)	.46	0.76 (0.42-1.40)	.38
BMI				
<24.99	1		1	
25-29.99	1.02 (0.63-1.64)	.95	0.98 (0.60-1.58)	.92
30-34.99	0.91 (0.51-1.62)	.75	0.86 (0.48-1.53)	.61
>35	1.84 (0.58-5.87)	.30	1.73 (0.54-5.58)	.36
Age at diagnosis (y)				
0-11	1		**1**	
12-39	1.67 (1.00-2.81)	.052	**1.77 (1.05-3.00)**	**.033**
40-69	**6.23 (2.25-17.29)**	**<.001**	**7.04 (2.49-19.87)**	**<.001**
Time from asthma diagnosis (y)				
≥20	1		1	
10-19	1.21 (0.69-2.13)	.51	1.11 (0.63-1.97)	.71
0-9	**2.29 (1.04-5.04)**	**.039**	2.10 (0.95-4.63)	.067
Exercise ≥2-3 times per week	1.40 (0.91-2.17)	.13	1.38 (0.89-2.15)	.15
Allergic rhinitis	**2.38 (1.56-3.63)**	**<.001**	**2.42 (1.58-3.71)**	**<.001**
Age (y)				
60-69	1		1	
50-59	1.27 (0.59-2.73)	.54	1.43 (0.65-3.12)	.38
40-49	0.92 (0.43-1.97)	.84	0.96 (0.44-2.06)	.91
30-39	0.76 (0.35-1.62)	.47	0.79 (0.37-1.70)	.55
20-29	1.05 (0.42-2.61)	.91	1.21 (0.48-3.06)	.68
Coexisting COPD	**5.35 (1.22-23.48)**	**.026**	N/D	
Helsinki as habitat	0.99 (0.62-1.57)	.95	0.97 (0.60-1.55)	.89

BMI, Body mass index; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *OR*, odds ratio.
Bolded text indicates statistical significance ($P < .05$).
*Two different multiple logistic regression analyses were conducted with a target variable of remission of asthma. Nonremission was coded as 1 and remission as 0. Reported ORs have been adjusted for all the variables listed.