Original Article

Atopy Modifies the Association Between Inhaled Corticosteroid Use and Lung Function Decline in Patients with Asthma

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What is already known about this topic? Inhaled corticosteroids are the mainstay of asthma treatment, but response to medication is variable.

What does this article add to our knowledge? Lung function decline over 2 decades was slower for adults with atopic asthma under sustained inhaled corticosteroid treatment compared with their nonatopic peers.

How does this study impact current management guidelines? Biomarkers of allergic inflammation could be useful to predict long-term response to inhaled corticosteroids among patients with asthma.

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Abbreviations used
BMI- Body mass index
ECRHS- European Community Respiratory Health Survey
FVC- Forced vital capacity
HDM- House-dust mite
ICS- Inhaled corticosteroid
IQR- Interquartile range
LABA- Long-acting β_2-agonist

BACKGROUND: Inhaled corticosteroids (ICSs) are the mainstay of asthma treatment, but response to medication is variable. Patients with allergic inflammation generally show a better short-term response to ICSs; however, studies on predictors of long-term response are few.
OBJECTIVE: To assess whether allergic sensitization can modify the association between ICS use and lung function decline over 20 years in adult asthma.
METHODS: We used data from the 3 clinical examinations of the European Community Respiratory Health Survey. We measured ICS use (no use, and use for <1.3, 1.3-8, and >8 years) and FEV_1 decline among subjects with asthma over the 2 periods between consecutive examinations. We conducted a cohort study combining data of the 2 periods (906 observations from 745 subjects) to assess whether the association between ICS use and FEV_1 decline was modified by allergic sensitization (IgE > 0.35 kU/L for any of house-dust mite, timothy grass, cat, or *Cladosporium*).
RESULTS: FEV_1 decline was similar for non-ICS users, as well as ICS users for less than 1.3 years, with and without allergic sensitization. However, among subjects on ICSs for a longer period, sensitization was associated with an attenuated decline ($P_{interaction}$ = .006): in the group treated for more than 8 years, FEV_1 decline was on average 27 mL/y (95% $CI_{Bonferroni\text{-}adjusted}$, 11-42) lower for subjects with sensitization compared with nonsensitized subjects.
CONCLUSIONS: Our study suggests that biomarkers of atopy can predict a more favorable long-term response to ICSs. Randomized controlled studies are needed to confirm these findings. **© 2019 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).**
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Key words: *Allergic sensitization; Asthma; Atopy; Cohort study; Epidemiology; IgE; Inhaled corticosteroids; Lung function decline; Precision medicine; Response to corticosteroids*

INTRODUCTION

Inhaled corticosteroids (ICSs) are the mainstay of asthma treatment. Daily ICS use is recommended for persistent asthma, although 2 of 3 patients with persistent asthma do not take ICSs on a regular basis.[1]

ICSs can reduce airway inflammation, respiratory symptoms, exacerbations, and mortality in patients with asthma.[2-6] Established evidence from clinical trials shows that ICSs can improve lung function in the short-term.[4,5] A number of cohort studies on subjects with asthma have also shown that ICSs can attenuate the decline in lung function over periods of 10 to 20 years.[7-11] Some of these studies suggested a clinical benefit from early initiation and regular use,[10] and others documented exposure-response associations for a higher dose[7] or a longer period of treatment.[9]

Clinical response to ICSs is variable, and identifying biomarkers of response can improve therapeutic decisions.[12,13] In a previous analysis of data from the first 2 waves of the European Community Respiratory Health Survey (ECRHS I and II), we showed that an increased duration of ICS therapy was associated with an attenuated 10-year decline in lung function only among subjects with a high level of total serum IgE at baseline.[9] Participants in the ECRHS have now been followed for a further 10 years.

In the present study, we used the data collected from this third study wave (ECRHS III) to investigate whether, among subjects with asthma, sensitization to airborne allergens modifies the association between treatment with ICSs and lung function decline over 20 years. Secondarily, we aimed to replicate the previous analysis in a larger sample and over the extended follow-up period.

METHODS

Population and study design

ECRHS is an international cohort study on subjects from the general population aged 20 to 44 years at enrollment in the period 1991 to 1993.[14] At ECRHS I, a 20% random sample of participants in a postal screening (stage 1) was invited to take part in a clinical assessment (stage 2). In addition, a "symptomatic sample" consisting of those who reported respiratory symptoms, asthma attacks, or use of asthma medication in stage 1 was also invited. Participants were followed up in the periods 1999 to 2002 (ECRHS II)[15] and 2010 to 2013 (ECRHS III).[16] Ethical approval was obtained for each center from the appropriate ethics committees. Written informed consent was obtained from participants.

Current asthma was defined as having reported physician-diagnosed asthma and at least 1 of the following: asthma-like symptoms (wheeze, nocturnal chest tightness, attacks of breathlessness after activity/at rest/at nighttime), asthma attacks, use of inhaled/oral medicines for breathing problems in the last 12 months, or current use of inhalers, aerosols, or tablets for asthma.

The present cohort study covers an overall period of about 20 years between ECRHS I and III. To maximize the use of available information, we estimated the duration of ICS use and lung function decline among subjects with current asthma for the 2 follow-up periods between ECRHS I and II ("first period") and between ECRHS II and III ("second period"). Throughout the article, we use the terms "baseline" and "end" to indicate the beginning point and the ending point of a period, respectively. Participants with current asthma at ECRHS I were eligible for inclusion in both periods. Participants with current asthma at ECRHS II but not at ECRHS I were eligible for the second period only. See a flowchart of eligible participants in Appendix E1 in this article's Online Repository at www.jaci-inpractice.org.

Clinical measurements

Subjects were advised to avoid using a β_2-agonist or anticholinergic inhaler for 4 hours or oral medication (β_2-agonist, theophylline, or antimuscarinic) for 8 hours before the clinical tests. Time since the most recent use of a long-acting β_2-agonist (LABA) was recorded, and spirometric measurements from subjects who had used LABAs within the previous 12 hours were excluded. FEV_1 and forced vital capacity

(FVC) repeatable to 150 mL were measured from at least 2 technically satisfactory maneuvers, according to the American Thoracic Society recommendations.[17] Biomedin (Biomedin, Padova, Italy) or SensorMedics (SensorMedics, Yorba Linda, Calif) spirometers were used in most centers at ECRHS I and II, whereas NDD EasyOne (ndd Medical Technologies, Zurich, Switzerland) was used in all centers at ECRHS III except for Verona and Torino.[18] A set of lung function measurements corrected for change in spirometer was also derived according to Bridevaux et al[19] and used for a sensitivity analysis. Height and weight were measured and body mass index (BMI) was calculated (kg/m^2). At ECRHS I and II, serum levels of total IgE and specific IgE to house-dust mite (HDM), timothy grass, cat, or *Cladosporium* were measured using the Pharmacia CAP system (Pharmacia, Uppsala, Sweden).[16] Concentrations of total IgE above 100 kU/L were considered to be high.[9] Sensitization to an allergen was considered present when specific IgE levels were above 0.35 kU/L, the detection limit of the assay. We considered allergic sensitization, defined as sensitization to at least 1 among the 4 allergens, as effect modifier in the main analysis.

Questionnaire data

At each time point, detailed information on asthma status, lifestyle, and risk factors was collected through personal interviews, and prebronchodilator spirometry was performed. The participants were asked the type of inhaled/oral medication for breathing problems they used in the last 12 months. In ECRHS II and III, participants were asked whether they had ever used ICSs, and they could point at the medication used in a list shown by trained interviewers. Among users, we estimated the duration of ICS therapy during each period on the basis of number of years of use ("used every year since the last survey?"; if not, "how many of the years since the last survey?") and the average number of months of use per year. Finally, participants were grouped into nonusers and users for less than 1.3 years, 1.3 to 8 years, and more than 8 years, on the basis of tertiles of therapy duration calculated over both periods. We used information available at each time point about adherence to "medication prescribed for breathing problems" to construct a proxy indicator of adherence to ICSs. Subjects were considered to be adherent during a follow-up period if they reported to normally take all/most of prescribed medicines both at baseline and at end of the period.

Statistical analysis

We described the characteristics of subjects with current asthma separately for the 2 periods. Then, we pooled the data from the 2 periods and conducted a combined analysis. The main outcome was decline in FEV_1 in milliliter per year during a period [($FEV_{1baseline} - FEV_{1end}$)/time, with positive values representing decline], which we analyzed using 3-level random-intercept linear regression models, with observations (level 1) nested into subjects (level 2) to account for repeated measures, and subjects nested into centers (level 3). We tested whether clustering by center significantly improved model fitting using likelihood ratio tests. The models included the following level 1 variables (1 observation per period): indicator of period (first/second); age, height, BMI, BMI^2 and allergic sensitization at baseline; duration of ICS therapy; annual change in BMI (ΔBMI),[20] and smoking status. The latter was coded as nonsmoker (never/past smoker at baseline and follow-up), transient smoker (current smoker either at baseline or end of a period), or current smoker (current smoker at both time points). The continuous variables were centered at the mean calculated over both periods. An interaction term between duration of ICS therapy and allergic sensitization was included *a priori*.[9] The models also included sex, education level (low if completed before age 16 years) as a proxy of socioeconomic status, and age at asthma onset (<18 vs ≥18 years) as level 2 variables (1 observation per subject). Missing data on adjustment variables were deleted listwise.

We replicated the main analysis:

1. adjusting for a multiple propensity score, obtained using multinomial logistic regression, and appropriate interaction terms (see Appendix E2 in this article's Online Repository at www.jaci-inpractice.org)[21];
2. modeling duration of ICS therapy as a quantitative variable, using a method to estimate the exposure-response function for a continuous exposure with a large proportion of unexposed subjects (see Appendix E3 in this article's Online Repository at www.jaci-inpractice.org)[22];
3. further adjusting for use of oral corticosteroids or asthma attacks in the previous 12 months (asthma severity) at baseline; use of LABAs (use in the previous 12 months reported: never, at baseline of a period, at end of a period, at both time points); occupational exposure to vapors, gas, dust, or fumes during a period (in months), which was reconstructed on the basis of participants' previous and present occupations, and weighted for intensity of exposure as explained elsewhere[23];
4. restricting the analysis to subjects adherent to prescribed medication;
5. using total serum IgE (high/low) and sensitization to each allergen at baseline (instead of allergic sensitization) as indicators of atopy in separate models; and
6. analyzing alternative outcomes:
   - decline in FEV_1/FVC (%/y) = 100 × ($FEV_1/FVC_{baseline} - FEV_1/FVC_{end}$)/time;
   - decline in FVC (mL/y) = ($FVC_{baseline} - FVC_{end}$)/time;
   - decline in FEV_1 % of baseline value (%/y) = 100 × [($FEV_{1baseline} - FEV_{1end}$)/$FEV_{1baseline}$]/time;
   - decline in FEV_1 (mL/y) calculated using measurements corrected for change in spirometer.[19]

Adjusted mean decline in lung function was calculated by setting quantitative and indicator variables equal to the mean and proportion, respectively (calculated over the set of subjects in each analysis). The statistical analyses were performed using STATA software, release 15.1 (StataCorp, College Station, Texas).

RESULTS

There were 17,943, 10,781, and 6841 participants in ECRHS I, II, and III, respectively, from 28 centers; about 85% were from the random sample (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). The numbers of subjects with current asthma eligible to be included in the first and second periods were 1189 and 1131, respectively (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). After excluding subjects due to loss to follow-up or missing data, 522 and 384 subjects contributed data to the first and second period, respectively, totaling 906 observations from 745 subjects (161 participants contributed data to both periods) (Figure 1). The distribution of subjects by center is presented in Table E2 in this article's Online Repository at www.jaci-inpractice.org.

The subjects included were slightly older and less likely to smoke or use ICSs at baseline compared with those excluded (Table I).

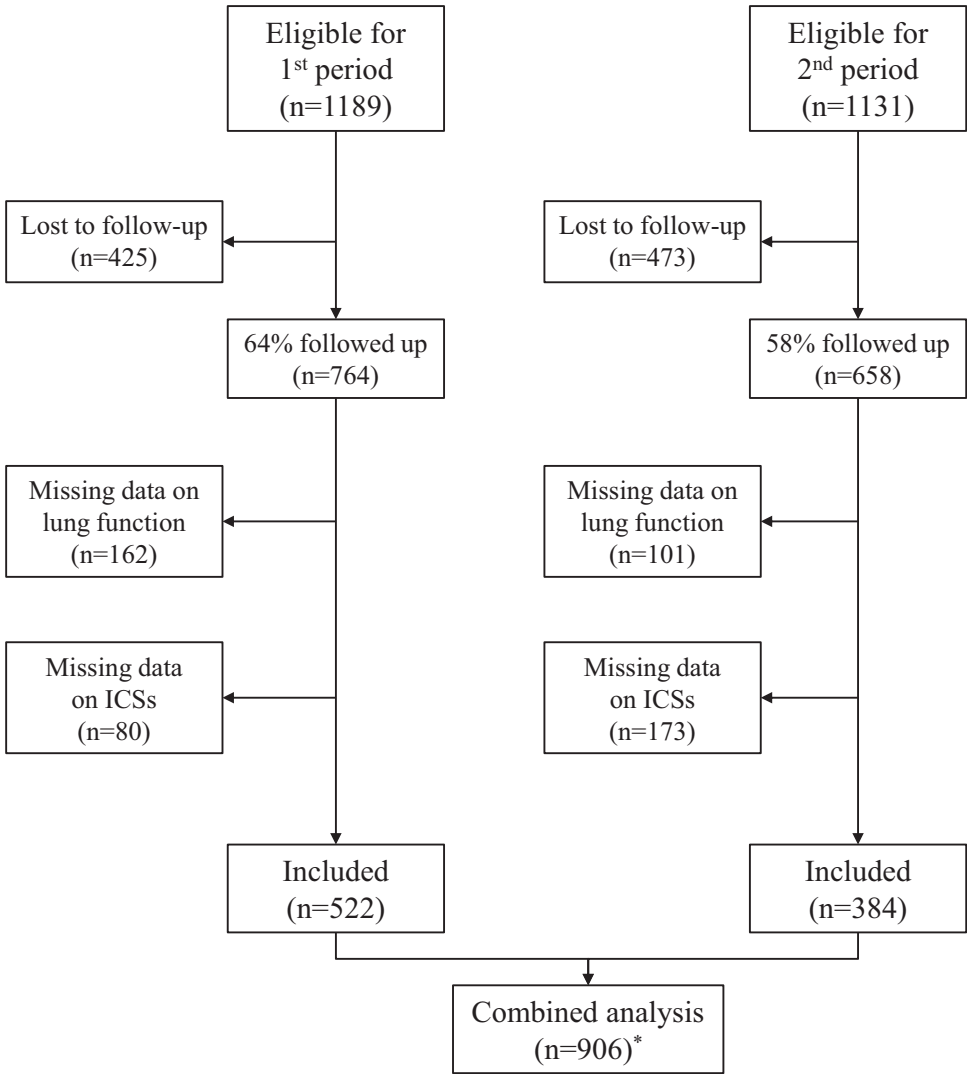

FIGURE 1. Flowchart of the study. *From 745 participants (161 participants contributed data to both periods).

The median follow-up time was 8.7 years (range, 6.1-11.2 years) for the first period and 11.6 years (range, 8.6-15.3 years) for the second. ICS users were 246 (47%) during the first period and 231 (60%) during the second period. Median duration of therapy among users was 2.7 years (interquartile range [IQR], 0.7-8.2 years) and 4.9 years (IQR, 1.0-10.8 years), respectively.

Because of the inclusion of subjects with new-onset asthma at ECRHS II (see Appendix E1 in this article's Online Repository at www.jaci-inpractice.org), age at asthma onset was higher in the second period (mean, 20.1 ± 13.6 years) compared with the first (mean, 17.1 ± 12.5 years) (Table II). For all the allergens, the frequency of sensitization was lower in the second period compared with the first. In both periods, ICS use was more common in women and in those who were older when their asthma began, had a family history of asthma, and had a higher total serum IgE level (Table II). ICS users were more likely to be sensitized and less likely to be a current smoker at baseline.

Increased duration of ICS therapy was strongly associated with several dimensions of severity at baseline, including a lower lung function and more frequent use of rescue and controller medication (Table III). Within each treatment group, subjects with sensitization had lower lung function and they were more likely to have symptoms or use short-acting β_2-agonists at baseline, compared with nonsensitized subjects (Table III).

Median unadjusted decline in FEV_1 was 30 mL/y (IQR, 10-52 mL/y) during the first period and 37 mL/y (IQR, 24-55 mL/y) during the second. Considering the 2 periods together (906 observations from 745 participants), decline in FEV_1 was 33 mL/y (IQR, 16-51 mL/y) and 36 mL/y (IQR,18-56 mL/y) for subjects with and without allergic sensitization, respectively. Among sensitized subjects, unadjusted decline in FEV_1 was lower for individuals who had used ICSs for a longer time ($P_{trend} = .001$), ranging in median from 35 mL/y (IQR, 19-51 mL/y) among nonusers to 27 mL/y (IQR, 0-49 mL/y) among users for more than 8 years. However, this association was not seen among nonsensitized subjects ($P_{trend} = .12$): median decline was 36 mL/y (IQR, 1856 mL/y) among nonusers and 37 mL/y (IQR, 21-67 mL/y) among ICS users for more than 8 years.

TABLE I. Baseline participant characteristics by inclusion status in the analyses and period*

	First period		Second period	
Characteristic	**Excluded† (n = 667)**	**Included (n = 522)**	**Excluded† (n = 747)**	**Included (n = 384)**
Sex: female, n (%)	378 (56.7)	283 (54.2)	444 (59.4)	225 (58.6)
Low education, n (%)	85 (14.1)	70 (13.4)	97 (13.0)	51 (13.3)
Smoking habits, n (%)				
Nonsmoker	283 (42.6)	242 (46.4)‡	352 (47.4)	167 (43.7)
Ex-smoker	133 (20.0)	123 (23.6)	205 (27.6)	122 (31.9)
Current smoker	248 (37.4)	157 (30.1)	185 (24.9)	93 (24.4)
Age (y), mean ± SD	34.9 ± 6.1	35.6 ± 6.2‡	41.9 ± 7.3	42.5 ± 6.9
BMI (kg/m^2), mean ± SD	24.6 ± 4.7	24.2 ± 4.2	26.1 ± 5.3	26.3 ± 5.0
FEV_1 (L), mean ± SD	3.3 ± 0.9	3.4 ± 0.8‡	3.2 ± 0.8	3.2 ± 0.8
%FEV_1/FVC, mean ± SD	77.7 ± 10.0	77.3 ± 9.7	76.7 ± 9.2	77.3 ± 8.2
Use of ICSs in the previous 12 mo, n (%)	217 (35.0)	99 (21.2)§	409 (55.5)	161 (42.4)§
Allergic sensitization, n (%)	377 (66.3)	306 (65.4)	449 (64.3)	225 (61.8)

*Statistics calculated on subjects with complete data; baseline refers to the start of the period.
†Subjects who were lost to follow-up or did not have complete data on lung function or ICS use.
‡$P < .05$, for comparison of excluded vs included; obtained using Pearson χ^2 test (categorical variables) and Student t test (quantitative variables).
§$P < .001$ for comparison of excluded vs included; obtained using Pearson χ^2 test (categorical variables) and Student t test (quantitative variables).

TABLE II. Baseline characteristics of ICS users and nonusers, by period*

	First period			Second period		
Characteristic	**Overall (N = 522)**	**Non-ICS users (n = 276)**	**ICS users (n = 246)**	**Overall (N = 384)**	**Non-ICS users (n = 153)**	**ICS users (n = 231)**
Sex: female, n (%)	283 (54.2)	129 (46.7)	154 (62.6)†	225 (58.6)	78 (51.0)	147 (63.6)‡
Low education, n (%)	70 (13.4)	34 (12.4)	36 (14.6)	51 (13.3)	16 (10.5)	35 (15.2)
Current smoking, n (%)	157 (30.1)	101 (36.6)	56 (22.8)§	93 (24.4)	42 (27.5)	51 (22.1)
Age (y), mean ± SD	35.6 ± 6.2	35.5 ± 6.1	35.7 ± 6.3	42.5 ± 6.9	42.1 ± 6.8	42.7 ± 7.0
BMI (kg/m^2), mean ± SD	24.2 ± 4.2	23.9 ± 3.8	24.5 ± 4.7	26.3 ± 5.0	25.5 ± 4.3	26.7 ± 5.4‡
Age at asthma onset (y), mean ± SD	17.1 ± 12.5	15.7 ± 12.2	18.6 ± 12.5§	20.1 ± 13.6	17.9 ± 13.1	21.6 ± 13.8‡
Family asthma, n (%)	124 (25.6)	51 (19.9)	73 (32.0)§	102 (28.2)	37 (26.4)	65 (29.3)
Total IgE, geometric mean ± SD	78.7 ± 4.8	71.4 ± 4.5	87.8 ± 5.1	73.6 ± 4.2	56.5 ± 4.8	86.6 ± 3.8§
Cat sensitization, n (%)	164 (35.0)	70 (28.3)	94 (42.5)†	119 (32.6)	36 (25.9)	83 (36.7)‡
Cladosporium sensitization, n (%)	58 (12.4)	22 (8.9)	36 (16.3)‡	12 (3.3)	4 (2.9)	8 (3.5)
Grass pollen sensitization, n (%)	196 (41.9)	98 (39.7)	98 (44.3)	131 (36.0)	48 (34.8)	83 (36.7)
HDM sensitization, n (%)	179 (38.3)	90 (36.4)	89 (40.3)	115 (31.5)	49 (35.3)	66 (29.2)

*Statistics calculated on subjects with complete data; baseline refers to the start of the period.
†$P < .001$ for comparison of non-ICS users vs ICS users; obtained using Pearson χ^2 test (categorical variables) and Student t test (quantitative variables).
‡$P < .05$ for comparison of non-ICS users vs ICS users; obtained using Pearson χ^2 test (categorical variables) and Student t test (quantitative variables).
§$P < .01$ for comparison of non-ICS users vs ICS users; obtained using Pearson χ^2 test (categorical variables) and Student t test (quantitative variables).

Clustering by center significantly improved model fitting in all the adjusted analyses, although centers explained only a small percentage of total variability. As an example for the main analysis (Figure 2, *A*), the proportion of variability in FEV_1 decline explained by centers was 2.1%, that is, variance partitioning coefficient = 0.021 ($P = .016$). Decline in FEV_1 was similar for non-ICS users, as well as for users for less than 1.3 years, with and without allergic sensitization at baseline (Figure 2, *A*). However, for subjects under a longer therapy, decline in FEV_1 differed according to sensitization ($P_{interaction} = .006$). In the group treated for more than 8 years, sensitized patients had an attenuated decline in FEV_1 compared with nonsensitized patients, with an average difference between the 2 groups of 27 mL/y (95% $CI_{Bonferroni}$, 11-42). Results were consistent when the main analysis was repeated using a multiple propensity score method (Figure 2, *B*) or when considering duration of therapy as a quantitative variable (Figure 2, *C*). Results were also consistent when adjusting for indicators of baseline severity (see Figure E3, *A* and *B*, in this article's Online Repository at www.jaci-inpractice.org), concomitant use of LABAs (Figure E3, *C*), or occupational exposures (Figure E3, *D*).

Sensitized and nonsensitized subjects adherent to prescribed medication were 53.6% and 45.7%, respectively ($P = .04$).

TABLE III. Asthma severity and pharmacological treatment at baseline according to duration of ICS therapy, by allergic sensitization*

	Without allergic sensitization (n = 301)				With allergic sensitization (n = 531)			
Characteristic	Non-ICS users	Used for <1.3 y	Used for 1.3-8 y	Used for >8 y	Non-ICS users	Used for <1.3 y	Used for 1.3-8 y	Used for >8 y
No. of subjects	141	51	52	57	244	100	93	94
FEV_1 % predicted, mean ± SD	97.7 ± 12.2	94.1 ± 13.4	90.4 ± 16.5	89.0 ± 16.1†	95.2 ± 11.8	92.1 ± 14.3	88.0 ± 18.2	84.5 ± 16.5†
%FEV_1/FVC, mean ± SD	80.4 ± 7.2	77.5 ± 8.2	78.1 ± 8.3	75.8 ± 10.2‡	78.3 ± 8.0	76.0 ± 8.7	76.1 ± 9.5	71.8 ± 10.3†
Wheeze§, n (%)	82 (58.2)	41 (80.4)	35 (67.3)	46 (80.7)‡	182 (74.6)	81 (81.0)	80 (86.0)	79 (84.0)
Asthma attack§, n (%)	51 (36.2)	28 (57.1)	34 (65.4)	34 (59.6)†	110 (45.1)	60 (60.6)	66 (71.0)	60 (64.5)†
Use of oral corticosteroids§, n (%)	3 (2.2)	2 (4.1)	6 (11.8)	10 (18.2)‡	6 (2.6)	4 (4.4)	5 (5.9)	12 (13.3)‡
Use of short-acting β_2-agonists§, n (%)	34 (24.5)	28 (54.9)	29 (55.8)	44 (81.5)†	121 (50.0)	66 (68.0)	72 (83.7)	81 (89.0)†
Use of LABAs§,‖, n (%)	6 (4.4)	6 (11.8)	7 (13.7)	21 (40.4)†	10 (4.2)	11 (11.6)	13 (14.8)	33 (37.9)†
Use of leukotriene receptor antagonists§,‖, n (%)	0 (0.0)	0 (0.0)	2 (3.8)	4 (7.1)‡	0 (0.0)	1 (1.0)	1 (1.1)	2 (2.2)
Vaccinated for allergy§, n (%)	3 (2.1)	1 (2.0)	2 (3.8)	0 (0.0)	10 (4.1)	6 (6.1)	4 (4.4)	0 (0.0)

*Statistics calculated on subjects with complete data (n = 74 had missing data on sensitization); baseline refers to the start of the period.
†$P < .001$ for the overall comparison across groups; obtained using Pearson χ^2 or Fisher exact test (categorical variables) and ANOVA (quantitative variables).
‡$P < .01$ for the overall comparison across groups; obtained using Pearson's χ^2 or Fisher exact test (categorical variables) and ANOVA (quantitative variables).
§In the previous 12 mo.
‖Not in commerce at ECRHS I.

When the main analysis was restricted to subjects adherent to medication, the results were fully consistent (Figure 3).

A similar pattern of associations was seen when considering modification by total serum IgE (although less evident: $P_{interaction} = .063$; see Figure E4 in this article's Online Repository at www.jaci-inpractice.org), as well as modification by sensitization to each allergen separately (Figure 4). An exception was *Cladosporium*, likely due to having only 11 sensitized subjects who had taken ICSs for less than 1.3 years. Figure E5 in this article's Online Repository at www.jaci-inpractice.org illustrates how decline in FEV_1 was consistently attenuated for atopic versus nonatopic subjects treated with ICSs for more than 8 years, regardless of the indicator of atopy used to differentiate between the 2 groups.

When analyses were run with decline in FEV_1/FVC or decline in FVC as outcomes (see Figure E6, *A* and *B*, in this article's Online Repository at www.jaci-inpractice.org), the findings were broadly consistent but the interactions were not statistically significant.

DISCUSSION

In this large cohort study of adults with doctor-diagnosed current asthma followed over 2 decades, we found that, among those treated with ICSs for a longer period (>8 years), decline in FEV_1 was attenuated for subjects sensitized to any of 4 common aeroallergens (HDM, timothy grass, cat, and *Cladosporium*) compared with nonsensitized subjects. However, decline did not differ according to sensitization among subjects treated for a shorter period or non-ICS users. Consistent results were obtained when considering alternative indicators of atopy.

We used observational data obtained from representative samples of the general population in an international setting (28 centers in 13 countries). To better account for changes in ICS use between the 2 decades, the study was designed to cover 2 consecutive periods of about 10 years, rather than a single time interval, and the data from the 2 periods were analyzed jointly. This also maximized statistical power: for comparison, subjects with complete data over 20 years were only 161.

A major challenge in observational studies on drug effectiveness is that patients under medication generally have a more severe form of disease than untreated patients. This "confounding by indication" makes it difficult to disentangle the effects of treatment from the consequences of the disease. In our study, a longer period of ICS use was indeed associated with more severe asthma, as well as a lower lung function at baseline, which could also raise concerns regarding potential bias due to regression toward the mean. However, we highlight that comparisons between subjects with and without sensitization within each category of ICS use would only be marginally affected by these potential sources of bias. The results were fully consistent when using the propensity score method, which addresses directly indication for drug use by assessing comparability of subjects across treatment groups (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org).[21]

Among sensitized subjects, the decline in FEV_1 was lower for long-term ICS users (1.3-8 and >8 years), compared with nonusers and short-term users (Figure 2, *A*), despite the greater baseline severity of sustained users (Table III). This suggests that a sustained ICS use is able to mitigate the lung function effects of severe allergy-driven inflammation.[24,25] Asthma with allergic sensitization is associated with type 2 airway inflammation and eosinophilic endotypes.[26] ICSs are particularly effective in eosinophilic asthma,[12] because eosinophils are sensitive to the inhibitory effect of corticosteroids.[27-29]

Among nonsensitized subjects, in the main analysis, we observed increased lung function decline for those using ICSs for more than 8 years compared with nonusers or shorter time users (Figure 2, *A*), which could be due to the greater impact of chronic inflammation and airway remodeling in more severe asthma. Nonsensitized subjects are likely to include patients with noneosinophilic inflammation, which is less responsive to ICSs.

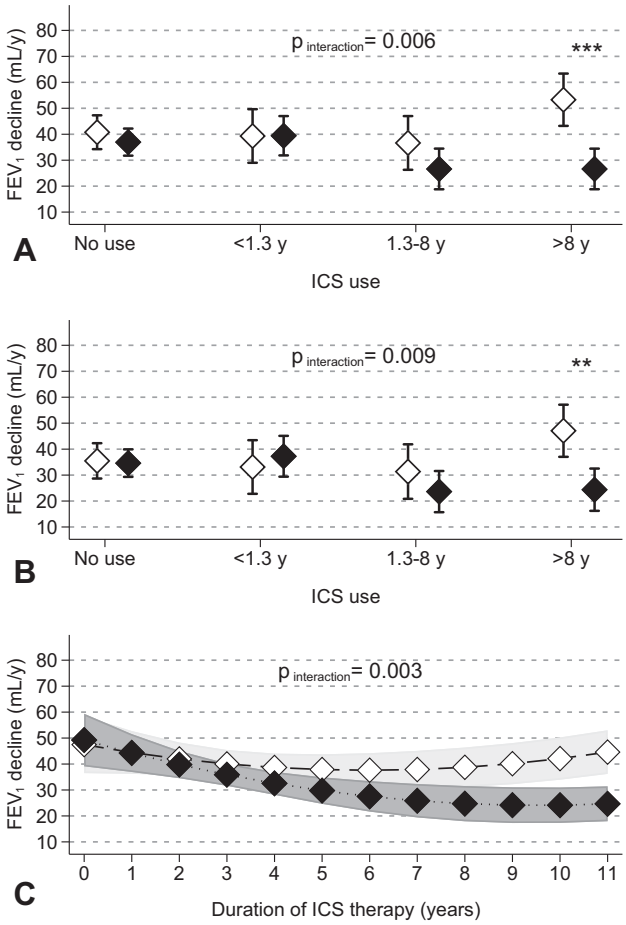

FIGURE 2. Adjusted mean decline in FEV_1 with 95% CIs by duration of ICS therapy during follow-up, for subjects with (solid symbols) and without (hollow symbols) allergic sensitization at baseline (**A**); sensitivity analyses using a multiple propensity score method (**B**) and considering therapy duration as a quantitative variable (**C**). $P_{interaction}$ is the overall P value for interaction between ICS use and sensitization obtained by Wald test; complete-case analysis: N = 812, 818, and 812, respectively. Panel B: adjusted for multiple propensity score and appropriate interaction terms, annual change in BMI, and current smoking status. Panel C: main independent variables were therapy duration (months), its interaction with sensitization, and therapy duration squared (months^2). $**P<.01$, $***P<.001$ for the comparison of subjects with vs without sensitization (Bonferroni adjustment for multiple testing).

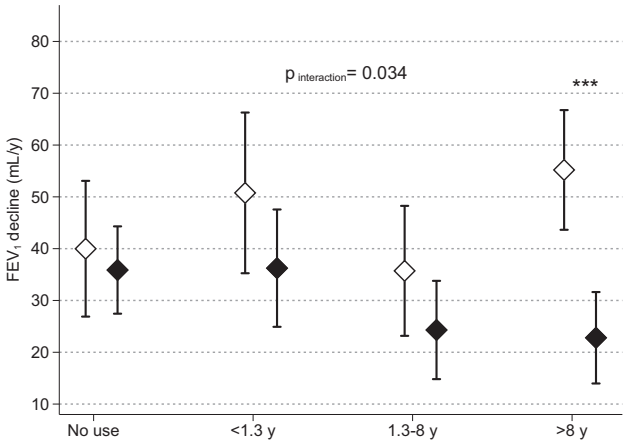

FIGURE 3. Adjusted mean decline in FEV_1 with 95% CIs by duration of ICS therapy during follow-up, for subjects with (solid symbols) and without (hollow symbols) allergic sensitization at baseline: analysis restricted to subjects adherent to prescribed medication for breathing problems. $P_{interaction}$ is the overall P value for interaction between ICS use and sensitization obtained by Wald test; complete-case analysis: N = 379. $***P<.001$ for the comparison of subjects with vs without sensitization (Bonferroni adjustment for multiple testing).

These results should not be interpreted as evidence for an adverse effect of ICSs, because ICSs have favorable effects on several other outcomes. Because of the observational nature of the study and the lack of randomization, our reasoning remains speculative.

We found a higher adherence to prescribed medication among subjects with allergic sensitization, which could be explained by a greater perceived benefit of treatment compared with their nonsensitized peers. Nonetheless, consistent results in the analysis restricted to adherent subjects rules out the hypothesis that differential adherence is a major explanation of our findings.

Our results were similar whatever marker of atopy was considered as an effect modifier, although in some cases the interactions were less evident. The most consistent finding was an attenuated decline in FEV_1 for atopic (vs nonatopic) subjects using ICSs for more than 8 years (Figure E5). The strongest interaction was observed for HDM sensitization ($P_{interaction} < .001$), whereas nonsignificant interactions were observed for cat and grass pollen sensitization ($P_{interaction} > .20$). Because the frequency of sensitization was similar for these 3 allergens in our sample (30%-40% regardless of the period), we believe that the stronger interaction seen for HDM is not related to statistical power. Recent research suggests that asthma related to HDM allergy could be particularly responsive to medication targeting IgEs or eosinophils.[30,31]

The associations observed for FEV_1/FVC ratio and FVC were consistent with what we found for FEV_1, except that the differences between sensitized and nonsensitized subjects were blunted (and the interactions were not significant). This could be linked to a greater response to ICSs for FEV_1 compared with FVC.

Because data on maximum attained lung function were not available, we did not adjust for baseline FEV_1 *a priori* to avoid overadjustment. In fact, the baseline time points in our study were ages during adult life (25-56 years) when FEV_1 can already be impaired as a consequence of previous accelerated decline. In this scenario, adjustment for FEV_1 could mask true differences.[32,33] Nonetheless, the results were consistent when analyzing FEV_1 % of baseline (Figure E6, *C*).

Study limitations

Self-reporting of asthma and use of medication is a limitation of the present study, although questionnaire-based definitions are highly specific and widely used in epidemiology.[34] To our knowledge, validation studies of self-reported duration of ICS

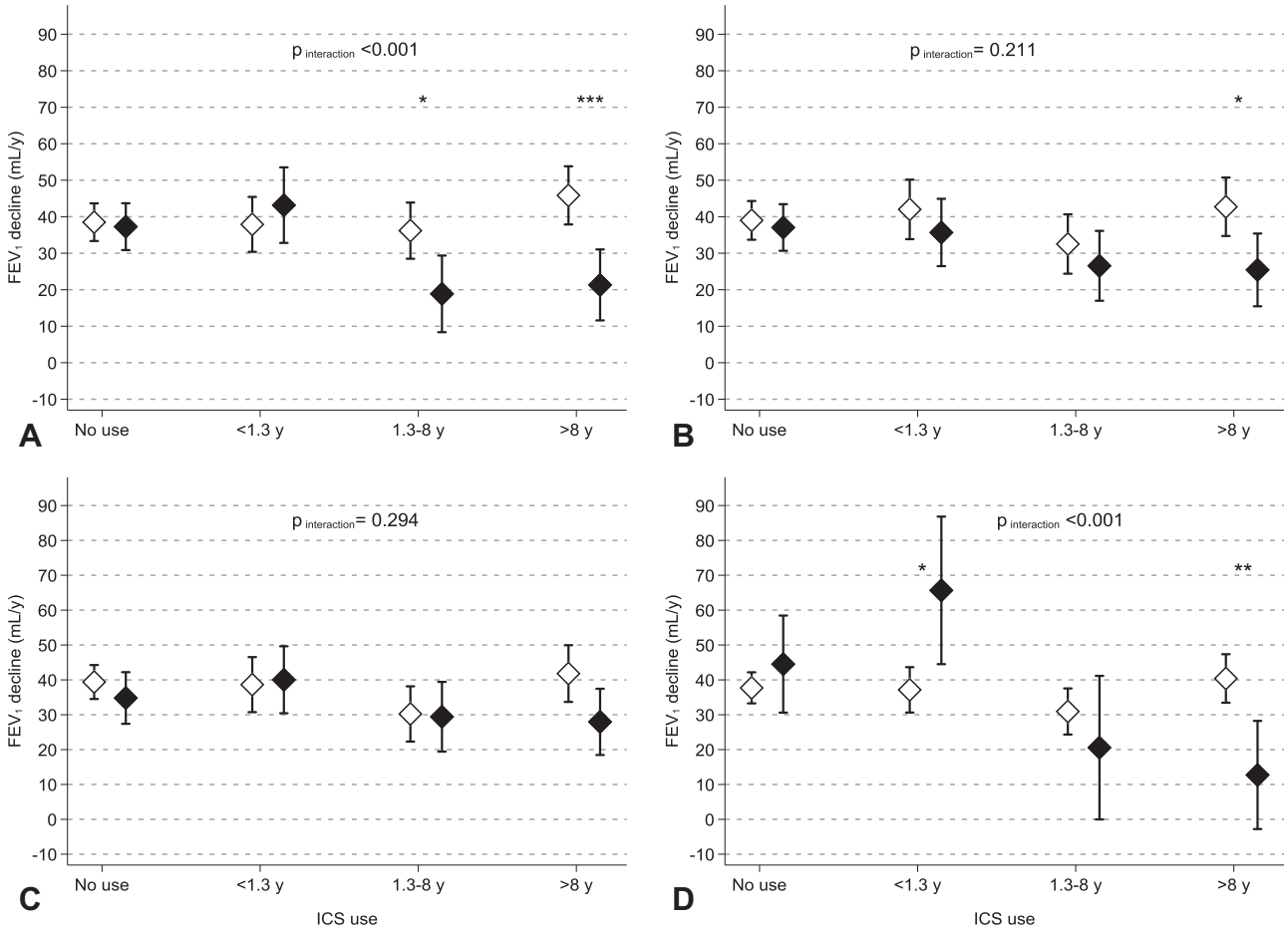

FIGURE 4. Adjusted mean decline in FEV_1 with 95% CIs by duration of ICS therapy during follow-up, for subjects with (solid symbols) and without (hollow symbols) sensitization to HDM, timothy grass, cat, or *Cladosporium* allergens at baseline (**A**-**D**, respectively). $P_{interaction}$ is the overall *P* value for interaction between ICS use and allergen-specific sensitization obtained by Wald test. Complete-case analysis: N = 812. $*P < .05$; $**P < .01$; $***P < .001$ for the comparison of subjects with vs without sensitization (Bonferroni adjustment for multiple testing).

therapy using pharmacy records have not been conducted. Aimed at improving the validity of self-reported information, we included a confirmation by a physician in the definition of asthma, as well as a report of current respiratory symptoms or use of medication. One further shortcoming is that we had no data to quantify the use of medication other than ICSs, which made it difficult to disentangle response to ICSs from response to other treatments. Nonetheless, very few subjects reported use of leukotriene receptor antagonists or vaccination for allergy (Table III), and the analysis adjusted for use of LABAs was consistent. As in other epidemiological studies spanning across decades, spirometers were changed in many centers for logistic reasons. We are aware that performance can change when using different instruments. However, the sensitivity analysis on FEV_1 corrected for change in spirometer was completely consistent with the main analysis (Figure E6, *D*). We also acknowledge as a limitation the lack of measures of decline based on post-bronchodilator lung function. Because of nonparticipation and missing data, we had to exclude a number of subjects from the analyses. However, the baseline distributions of the main variables under study (FEV_1 and sensitization) were similar between included and excluded subjects. The latter were more likely to report a history of ICS use compared with those included, but this is because some ICS users failed to provide additional information on duration of therapy. Finally, we did not have baseline data on other biomarkers that could be a promising guide for asthma treatment, such as blood or sputum eosinophils or exhaled nitric oxide.[35-37]

CONCLUSIONS

Our study adds further evidence to the lung function benefit of ICSs for patients with asthma, and suggests that indicators of atopy could be useful to predict the long-term response to sustained ICS treatment. Allergy tests could provide useful biomarkers for clinical decisions regarding asthma therapy and contribute to the advocated "precision medicine" approach in the treatment of chronic airway diseases.[35] Analyses from randomized controlled studies are needed to clarify this.

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Other Workpackage leaders in the ALEC study are Cecilie Svanes, John Henderson (Department of Community-Based Medicine, University of Bristol, Bristol, United Kingdom), Nicole Probst-Hensch, and Cosetta Minelli (National Heart and Lung Institute, Imperial College London, London, United Kingdom). The principal investigators and team members of the original studies are reported in Appendix E4. The ALEC International Scientific Advisory Board is as follows: Marike Boezen (University Medical Center Groningen, University of Groningen, Groningen, The Netherlands); Bernice Elger (Institute for Biomedical Ethics, University of Basel, Basel, Switzerland); Bo Alexander Gleditsch (The Norwegian Asthma and Allergy Association, Oslo, Norway); Bas Heijmans (Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, The Netherlands); Isabelle Romieu (National Institute of Public Health, Cuernavaca, Mexico; and Emory University, Atlanta, Ga); and John Thompson (Department of Health Sciences, University of Leicester, Leicester, United Kingdom).

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ONLINE REPOSITORY

APPENDIX E1. FLOWCHART OF ELIGIBLE PARTICIPANTS

Participants with current asthma at ECRHS I were eligible for inclusion in both follow-up periods, except for subjects younger than 25 years who were excluded from the first period (because maximum lung growth is usually reached around that age). Participants with current asthma at ECRHS II but not at ECRHS I were eligible for the second period only. Subjects were eligible for the first period if they had current asthma at ECRHS I, were 25 years or older, and had lung function data at ECRHS I (n = 1189) (Figure E1, *A*). Subjects were eligible for the second period (Figure E1, *B*) (n = 1131)

- if they had current asthma at ECRHS I, took part in ECRHS II, and had lung function data at ECRHS II (n = 779);
- if they had "new" current asthma at ECRHS II (ie, current asthma at ECRHS II but not at ECRHS I) and had lung function data at ECRHS II (n = 352). This group was made up of
  - 285 subjects who had not reported "ever asthma" at ECRHS I; that is, they had new-onset asthma at ECRHS II: median age at diagnosis among 267 subjects with available information was 31 years (IQR, 20-40 years);
  - 67 subjects who had reported "ever asthma" at ECRHS I but did not fulfill the criteria for current asthma at ECRHS I because they lacked a physician diagnosis (n = 36) or did not report current symptoms/use of medication (n = 31): median age at diagnosis was 14 years (IQR, 5-23 years).

APPENDIX E2. SENSITIVITY ANALYSIS USING A MULTIPLE PROPENSITY SCORE METHOD TO ADJUST FOR POTENTIAL CONFOUNDERS

Propensity score (PS) methods are a set of techniques that can be used to balance a set of covariates across treatment groups in observational studies, aimed to simulate the balance generated by treatment randomization.[E1,E2] Multiple PS methods are an extension of the method to 3 or more treatment groups.[E1,E3] Separate PS models for each paired treatment comparison are created using a multinomial logistic regression model.

As suggested by others,[E2-E4] we tested for inclusion in the multiple PS only baseline covariates associated with the outcome (FEV_1 decline), and we included only those covariates that were significantly associated in univariate analyses ($P < .10$). In the following list of baseline variables tested, the variables selected are marked with an asterisk:

- period (first/second)*
- sex*
- education level (low/high)*
- age (years)*
- height (m)*
- BMI (kg/m^2)* and BMI^2 (kg^2/m^4)*
- smoking status (nonsmoker, past smoker, current smoker)*
- allergic sensitization (yes/no)*
- serum total IgE (low/high)
- age at asthma onset (<18 vs ≥18 years)
- asthma duration (years)
- family asthma (yes/no)
- occupation (manual, nonmanual, other/unknown)
- type of spirometer (SensorMedics volume-displacement; SensorMedics heated-wire; Vitalograph; Jaeger Masterscope; Biomedin; Spirotech)
- use of short-acting β_2-agonists in the last 12 months (yes/no)
- use of oral corticosteroids in the last 12 months (yes/no)
- asthma attacks in the last 12 months (yes/no)
- asthma-like symptoms in the last 12 months (yes/no)
- hospital/emergency rooms admission in the last 12 months (yes/no)

We calculated conditional predicted probabilities of belonging to each treatment group, that is, the PSs, using a multinomial logistic regression model with treatment group as the outcome and all selected variables as independent variables. We then compared visually overlap of different PSs across the 4 treatment groups to check that each subject had the same possibility of being in each treatment group; that is, subjects had a comparable indication for drug use ("positivity" assumption).[E2] Figure E2 shows that the distributions of the scores were similar across the 4 treatment groups, indicating that there were no major violations of the assumption. However, when excluding the subjects with nonoverlapping PSs (about 15% of the study sample), the results were also consistent (data not shown).

In our study with $k = 4$ treatment groups, we devised a multiple PS score consisting of 3 scores. In fact, for a k-level treatment, k scores are estimated and because they sum to 1, only $k - 1$ scores are considered for subsequent analyses. Scores 1 and 4 were the most strongly correlated (Pearson r coefficient = 0.78). Three of the scores (1, 2, and 3) and 2 of their interaction terms (1 × 2 and 1 × 3) were finally used for adjustment. Interaction 2 × 3 was not considered because it was strongly correlated with scores 2 and 3 ($r = 0.87$ and 0.84, respectively).

To check for balance across treatment groups *before* and *after* multiple PS correction, we fitted models without and with correction for multiple PS, respectively. We used linear, logistic, or multinomial logistic regression for quantitative, binary, and categorical covariates, respectively, with each covariate as the dependent variable and treatment as the independent variable.[E3] We tested the null hypotheses that all 3 ($k - 1$) regression coefficients for treatment group are jointly 0 using Wald tests. The table below reports P values from Wald tests on the difference in distribution of covariates across treatment groups (computed before and after correction for multiple PSs), showing that the multiple PSs were quite effective in balancing out differences in covariates across treatment groups.

We then repeated the main analysis using a 3-level model (centers/subjects/observations) adjusted for treatment group,

Baseline variable	Before correction (P value)	After correction (P value)
Period	<.001	.98
Sex	.001	.98
Education	.42	.94
Age (y)	<.001	.99
Height (m)	.02	.99
BMI (kg/m^2)	<.001	.98
Smoking status	.001	.99
Allergic sensitization	.91	.99

allergic sensitization (and their interaction), the multiple PSs (and interaction terms), annual change in BMI, and smoking status. The results, reported in Figure 2, *B*, were completely consistent with the main analysis.

APPENDIX E3. SENSITIVITY ANALYSIS CONSIDERING DURATION OF ICS THERAPY AS A CONTINUOUS MEASURE

For sensitivity analysis we considered duration of ICS therapy as a continuous measure. We modeled duration of ICS therapy using a method proposed to estimate the exposure-response function for a continuous exposure with a "spike" at 0, that is, a large proportion of unexposed subjects.[E5]

We added duration of therapy with a small constant (corresponding to 1 day of therapy) to avoid missing values for non-ICS users, as suggested by Royston et al,[E5] and centered at the mean value.

We then tested, both separately and in combination, 3 indicators of ICS use, with and without their interactions with allergic sensitization:

1. a dummy for ICS use during follow-up (yes/no);
2. duration of therapy (months);
3. duration of therapy squared (months^2), which was considered to account for possible nonlinear exposure-response associations.

Likelihood ratio tests were used to determine whether each parameter added significantly improved model fitting ($P < .10$). We used a 3-level model (centers/subjects/observations) and included the full set of adjustment variables.

The final model included therapy duration, its interaction with allergic sensitization, and therapy duration squared.

The results, which are reported in Figure 2, C, are consistent with the main analysis.

APPENDIX E4. SUPPLEMENTARY INFORMATION ON THE ECRHS

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†Deceased.

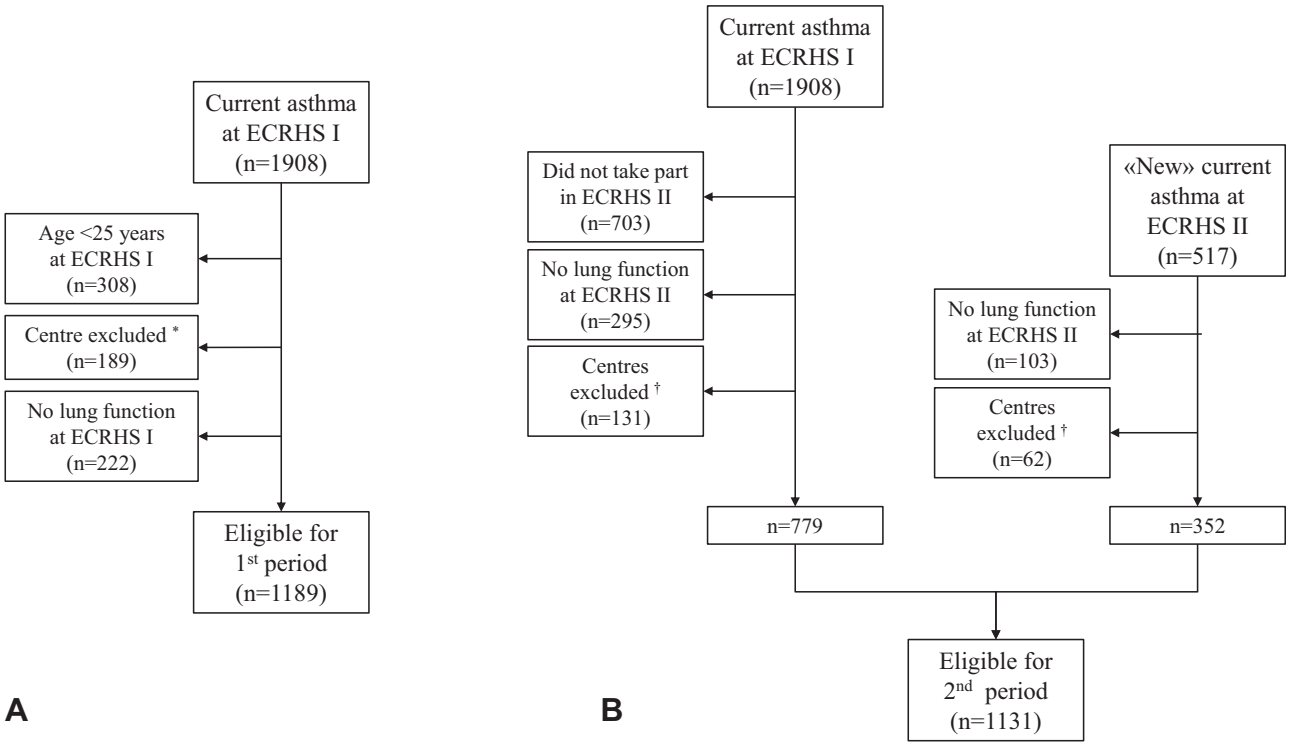

FIGURE E1. Flowcharts of subjects with current asthma who were eligible for inclusion in the first follow-up period (A) and in the second follow-up period (B). *Melbourne (no valid lung function at ECRHS I). †Cardiff and Portland (did not take part in ECRHS III), and Basel (did not collect data on ICS use at ECRHS III).

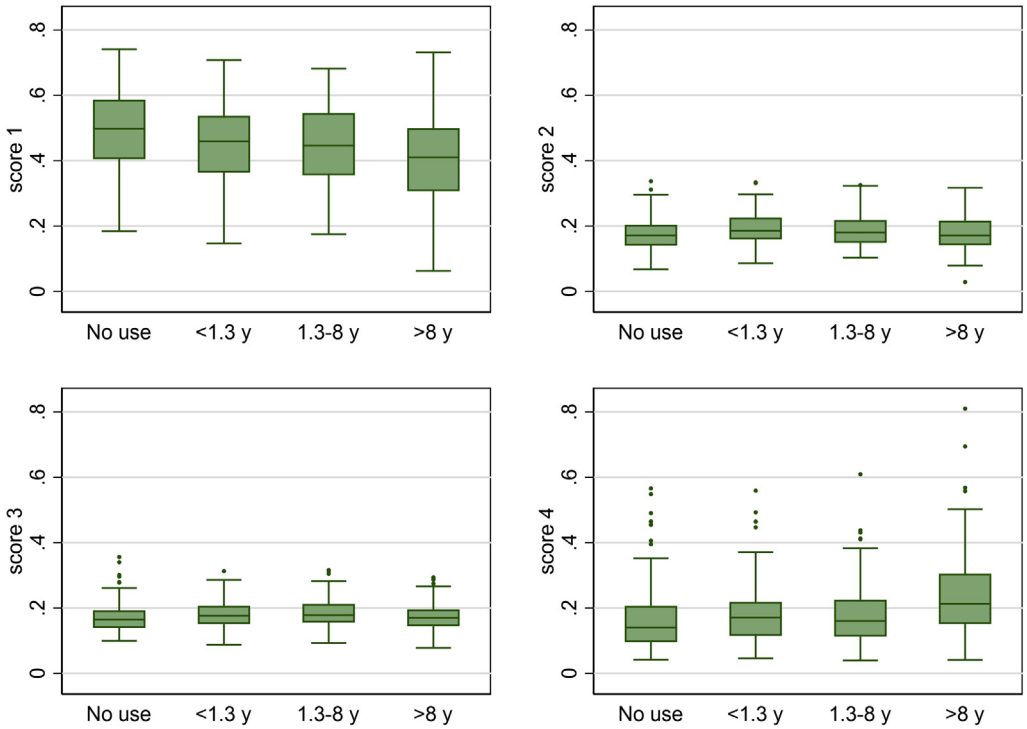

FIGURE E2. Box plots showing the overlap of the PSs across treatment groups.

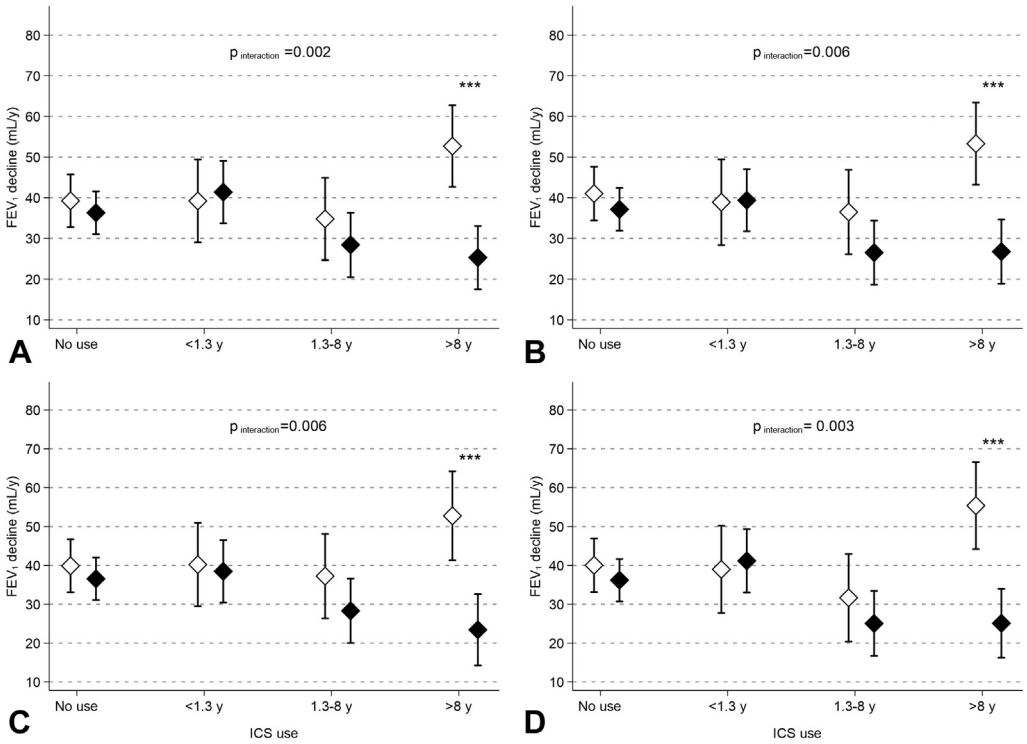

FIGURE E3. Adjusted mean decline in FEV_1 with 95% CIs by duration of ICS therapy, for subjects with (solid symbols) and without (hollow symbols) allergic sensitization at baseline. Sensitivity analyses with further adjustment variables. (**A**) Further adjusted for use of oral corticosteroid in the previous 12 months at baseline (N = 764). (**B**) Further adjusted for having had asthma attacks in the previous 12 months at baseline (N = 808). (**C**) Further adjusted for use of LABAs (4-level variable: use in the previous 12 months reported never/at baseline/at end/both at baseline and end of a period; N = 749). (**D**) Further adjusted for cumulative occupational exposure to vapors, gas, dust, or fumes during a period (N = 716). Baseline refers to the start of the period. $P_{interaction}$ is the overall *P* value for interaction between ICS use and sensitization obtained by Wald test. *** $P < .001$ for the comparison of subjects with vs without sensitization (Bonferroni adjustment for multiple testing).

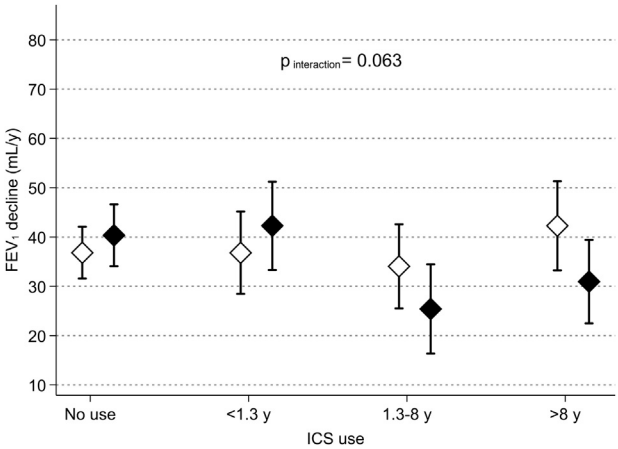

FIGURE E4. Adjusted mean decline in FEV_1 with 95% CIs by duration of ICS therapy during follow-up, for subjects with high (solid symbols) and low (hollow symbols) total serum IgE at baseline. $P_{interaction}$ is the overall *P* value for interaction between ICS use and total IgE level obtained by Wald test (N = 812).

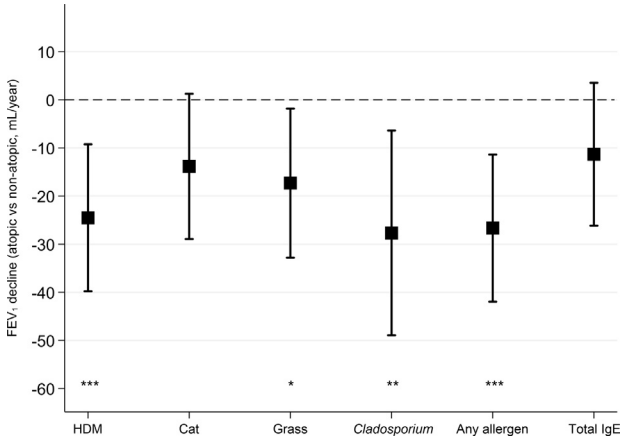

FIGURE E5. Adjusted mean difference in FEV_1 decline, with 95% CIs, between ICS users for more than 8 years with sensitization/high total IgE at baseline and ICS users for more than 8 years with no sensitization/low total IgE (reference). Baseline refers to the start of the period; negative values indicate attenuated decline for atopic subjects compared with nonatopic subjects. *$P < .05$; **$P < .01$; ***$P < .001$ (Bonferroni adjustment for multiple testing).

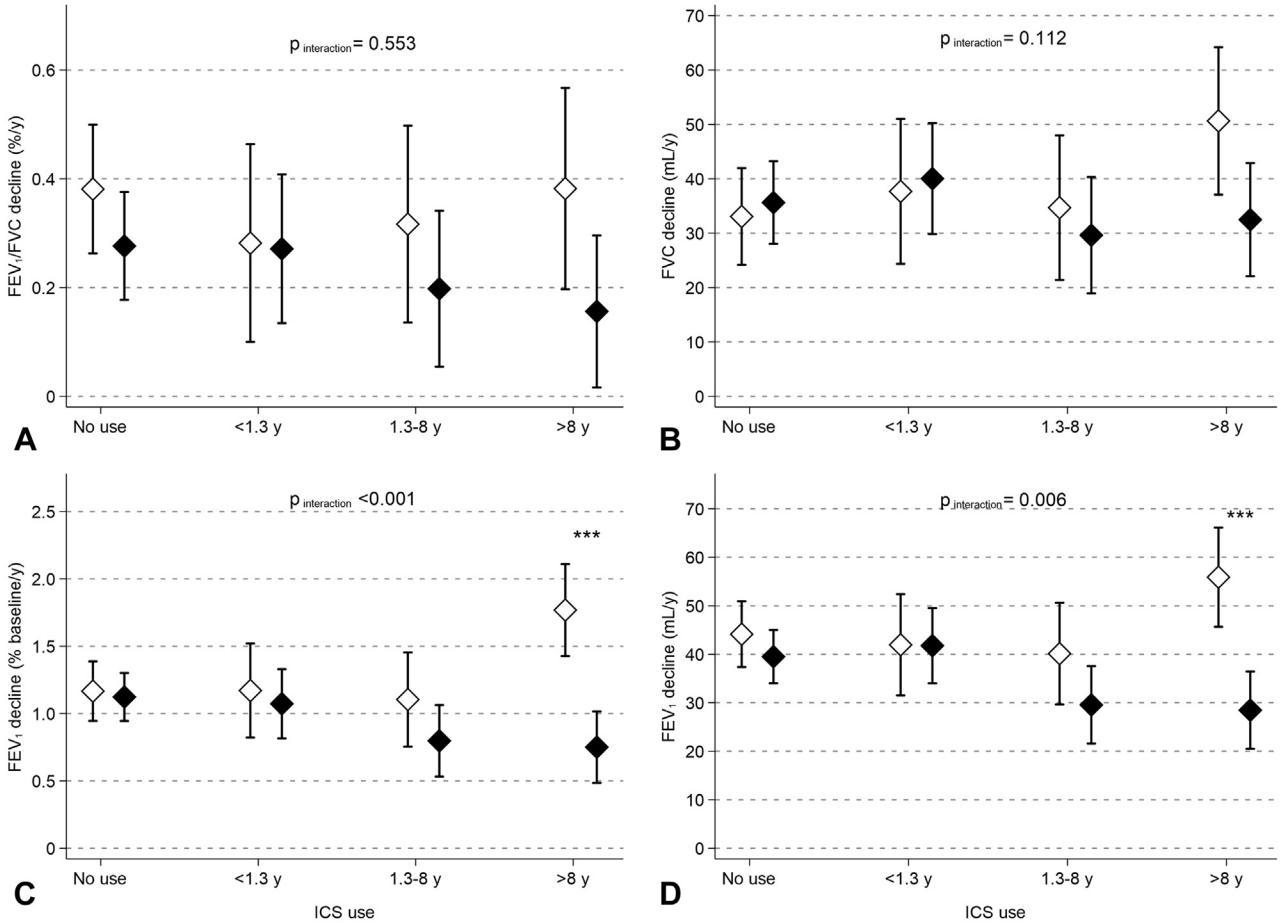

FIGURE E6. Adjusted mean decline in lung function with 95% CIs by duration of ICS therapy, for subjects with (solid symbols) and without (hollow symbols) allergic sensitization at baseline. Sensitivity analyses using alternative outcomes. (**A**) Decline in FEV_1/FVC (N = 742). (**B**) Decline in FVC (N = 742). (**C**) Decline in FEV_1 % of baseline value (N = 812). (**D**) Decline in FEV_1 calculated using measurements corrected for change in spirometer (N = 800). Baseline refers to the start of the period. $P_{interaction}$ is the overall P value for interaction between ICS use and sensitization obtained by Wald test. ***$P < .001$ for the comparison of subjects with vs without sensitization (Bonferroni adjustment for multiple testing).

TABLE E1. Number of participants in the clinical examinations, by center

Country	Center	ECRHS I (1991-1994)	ECRHS II (1999-2003)	ECRHS III (2010-2014)
Belgium	Antwerp City	651	333	194
	Antwerp South	634	386	170
Estonia	Tartu	558	328	165
Germany	Erfurt	731	287	336
	Hamburg	1,252	303	304
Spain	Albacete	626	449	244
	Barcelona	516	361	213
	Galdakao	592	443	385
	Huelva	403	306	156
	Oviedo	524	342	185
France	Bordeaux	544	165	206
	Grenoble	522	423	378
	Montpellier	456	202	187
	Paris	651	433	360
Italy	Pavia	310	192	77
	Turin	355	178	82
	Verona	360	219	99
Iceland	Reykjavik	647	524	453
Norway	Bergen	835	596	365
Sweden	Gothenburg	866	628	342
	Umea	708	543	297
	Uppsala	823	679	422
Australia	Melbourne	876	637	318
Switzerland	Basel	1,002	569	538
United Kingdom	Cardiff	519	332	0
	Ipswich	559	373	182
	Norwich	581	318	183
United States	Portland	842	232	0
	Random sample	15,303 (85%)	9,023 (84%)	5,904 (86%)
	Total	17,943	10,781	6,841

TABLE E2. Number of subjects with current asthma who were eligible for/included in the analyses, by follow-up period

		First period		Second period	
Country	**Center**	**Eligible**	**Included**	**Eligible**	**Included**
Belgium	Antwerp City	33	7	24	3
	Antwerp South	21	6	19	2
Estonia	Tartu	5	2	6	2
Germany	Erfurt	7	3	19	8
	Hamburg	36	6	23	13
Spain	Albacete	37	13	44	19
	Barcelona	30	12	36	11
	Galdakao	23	10	43	29
	Huelva	14	12	31	11
	Oviedo	20	9	32	15
France	Bordeaux	48	8	20	5
	Grenoble	45	33	55	25
	Montpellier	55	8	18	5
	Paris	43	24	40	12
Italy	Pavia	9	5	11	5
	Turin	30	14	22	7
	Verona	19	12	19	5
Iceland	Reykjavik	54	37	75	39
Norway	Bergen	37	24	65	19
Sweden	Gothenburg	69	32	76	26
	Umea	94	50	92	27
	Uppsala	80	44	97	41
Australia	Melbourne	0*	0	135	37
Switzerland	Basel	88	38	0†	0
United Kingdom	Cardiff	92	29	0‡	0
	Ipswich	71	37	56	10
	Norwich	70	34	73	8
United States	Portland	59	13	0‡	0
	Random sample	599 (50%)	249 (48%)	597 (53%)	201 (52%)
	Total	1189	522	1131	384

*Valid lung function measurements not available.
†Data on ICS use not collected at ECRHS III.
‡Did not take part in ECRHS III.

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