Can an airway challenge test predict respiratory diseases? A population-based international study

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Background: Evidence on the longitudinal association of airway responsiveness with respiratory diseases is scarce. The best indicator of responsiveness is still undetermined.
Objective: We investigated the association of airway responsiveness with the incidence of asthma, chronic obstructive pulmonary disease (COPD), and allergic rhinitis.
Methods: We studied 3851 subjects who underwent spirometry and methacholine challenge tests both at baseline (1991-1993), when they were 20 to 44 years old, and at follow-up (1999-2002) in the European Community Respiratory Health Survey. Airway responsiveness was defined based on the methacholine dose-response slope on both occasions. Incidence rate ratios for the association of airway responsiveness with disease occurrence were computed by using Poisson regression.
Results: With respect to reference (slope of the fourth quintile or greater), subjects with the greatest degree of airway responsiveness (slope less than the first quintile) showed the greatest risk of developing asthma, COPD, and allergic rhinitis (incidence rate ratios of 10.82, 5.53, and 4.84, respectively; all $P < .01$). A low slope predicted disease occurrence, even in subjects who did not reach a 20% decrease in FEV_1 at the cumulative dose of 1 mg of methacholine (PD_{20} >1 mg). A decrease in slope over time was an independent predictor of disease risk.
Conclusion: Airway responsiveness predicted new-onset asthma, COPD, and allergic rhinitis. Our study supports the use of a continuous noncensored indicator of airway responsiveness, such as the slope of the methacholine dose-response curve, in clinical practice and research because it showed clear advantages over PD_{20}. (J Allergy Clin Immunol 2013;■■■:■■■-■■■.)

Key words: *Airway hyperresponsiveness, airflow obstruction, allergic rhinitis, asthma, European Community Respiratory Health Survey, chronic obstructive pulmonary disease*

Airway responsiveness is frequently measured by administering increasing doses of a bronchoconstrictor, such as methacholine, which directly stimulates receptors on the airway smooth muscle.[1,2] The degree of airway responsiveness can be measured as the provocative dose or provocative concentration that produces a given percentage FEV_1 decrease, generally 10% or 20%.[3] A provocative dose or provocative concentration can only be estimated if a subject's FEV_1 decrease is greater than the given amount before the maximal dose is reached, and it is censored otherwise. This is why the test result is generally dichotomized and airway hyperresponsiveness (AHR) is considered to be present or absent. Airway responsiveness can also be assessed by using continuous noncensored indicators, such as the slope of the curve that describes the percentage decrease in FEV_1 by log dose of bronchoconstrictor.[4-6] Airway responsiveness is associated with atopy, airway inflammation, small airway caliber (low FEV_1), and respiratory symptoms.[7,8] Because it is present in almost all patients with current asthma, the absence of AHR can help to exclude the diagnosis.[9] Airway responsiveness is also associated with chronic obstructive pulmonary disease (COPD),[10] as well as COPD mortality, even among lifetime nonsmokers.[11] An association between allergic rhinitis and the onset of AHR has been reported,[12] but evidence for a causal relationship between the 2 conditions is still lacking. Airway responsiveness is not a stable feature over time.[13,14] It decreases through childhood,[15] and it generally increases in the elderly.[16] Changes in smoking habits can affect the degree of responsiveness.[17]

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Abbreviations used
AHR: Airway hyperresponsiveness
BMI: Body mass index
COPD: Chronic obstructive pulmonary disease
CV: Coefficient of variation
ECRHS: European Community Respiratory Health Survey
FVC: Forced vital capacity
GOLD: Global Initiative for Chronic Obstructive Lung Disease
IRR: Incidence rate ratio
LLN: Lower limit of normal

The main aims of this article are (1) to prospectively investigate the association of airway responsiveness at baseline with the risk of asthma, COPD, and allergic rhinitis and (2) to assess whether using a continuous noncensored indicator of responsiveness, such as slope, can be an advantage over a dichotomous indicator based on PD_{20}. For this purpose, the longitudinal data collected on random samples of the general adult population in the European Community Respiratory Health Survey (ECRHS) were analyzed.

METHODS

Study design

The ECRHS I is an international multicenter study performed between 1991 and 1993 on random samples of young adults (20-44 years of age) from the general population.[18] Each participant was sent a brief screening questionnaire (stage 1), and from those who responded, a random sample was selected to undergo a more detailed clinical examination (stage 2). The ECRHS II is a follow-up study of the subjects taking part in ECRHS I stage 2, which was performed between 1999 and 2002 (www.ecrhs.org).[19] Ethical approval was obtained for each center from the appropriate ethics committee, and written consent was obtained from the participants.

Maximum prebronchodilator FEV_1 and forced vital capacity (FVC) from at least 2 of up to 5 technically satisfactory maneuvers were measured at both surveys, according to the American Thoracic Society criteria for repeatability.[20] The lower limit of normal (LLN) was calculated on the basis of the equations by Cerveri et al[21] and obtained from healthy adults who participated in the ECRHS. A subject was considered sensitized to allergens if serum IgE levels for at least 1 allergen among house dust mite, cat dander, timothy grass, and *Cladosporium* species were greater than 0.35 kU/L.

Methacholine challenge tests were performed according to a standardized protocol on both occasions. FEV_1 was recorded 2 minutes after each inhalation, and in the absence of a 20% decrease in FEV_1 from baseline, the next dose was administered until the maximum cumulative dose of 1 mg was reached.[3] For each subject, the dose-response slope was calculated by regressing the percentage decrease in FEV_1 on a $\log_{10}$ dose (by using all the data except post-saline FEV_1) and then reciprocally transformed (100/[Dose-response slope + 10]) to satisfy the statistical assumptions of regression analysis.[4,22] Because lower levels of the transformed dose-response slope (called the slope from this point on) correspond to increased airway responsiveness, slope values are reported in descending order. Subjects were classified into 5 groups according to the quintiles of the baseline slope distribution. Subjects were also classified into 2 groups according to the PD_{20} threshold of 1 mg of methacholine.[3] Change in slope per year was computed as follows:

$$\Delta\text{Slope} = (\text{Slope}_1 - \text{Slope}_2)/(\text{Follow-up time}).$$

Outcomes

The outcomes analyzed were as follows: (1) for asthma, a positive answer to the question "Have you ever had asthma?"; (2) for COPD, an FEV_1/FVC ratio of less than the LLN in subjects who never reported asthma (ie, neither at baseline nor at follow-up); and (3) for allergic rhinitis, having both allergen sensitization and 1 of the criteria nasal allergies or hay fever, runny or stuffy nose, or sneezing in the presence of grass, trees, flowers, animals, or dust.[12]

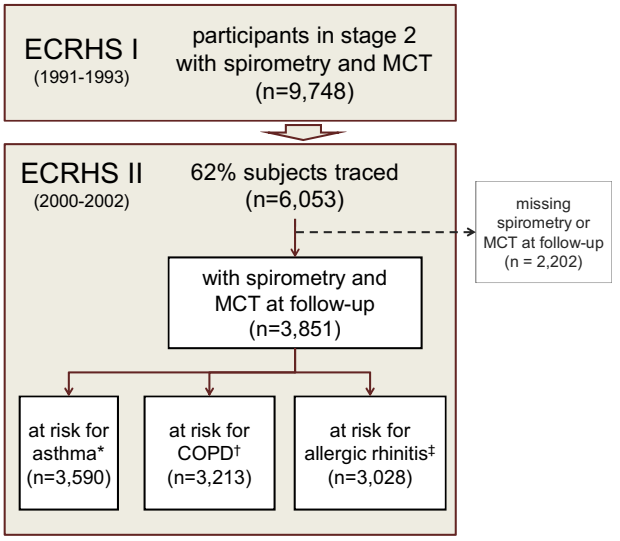

FIG 1. Number of subjects who were included in the analyses. *MCT,* Methacholine challenge test. *Free from asthma at baseline. †Free from COPD at baseline (and never reporting asthma). ‡Free from allergic rhinitis at baseline.

Sensitivity analyses were performed with different definitions of the diseases (including a definition of COPD based on the Global Initiative for chronic Obstructive Lung Disease [GOLD] criterion of an FEV_1/FVC ratio <0.70),[23] as well as analyzing different populations at risk (see the Methods section in this article's Online Repository at www.jacionline.org).

Statistical analyses

The potential confounders considered were sex, age, height, body mass index (BMI), FEV_1, education (low = completed before the age of 16 years), and allergen sensitization at baseline; season when the methacholine challenge test was performed at baseline and follow-up; moving to a new house ("Do you live in the same home as when you were last surveyed?"); annual change in BMI (ΔBMI) over follow-up; and lifetime smoking habits as follows: (1) nonsmoker at both surveys; (2) exsmoker at both surveys; smoker at both surveys with a history of (3) less than 15 pack years or (4) 15 or more pack years; (5) quitter (smoker who quit during follow-up); or (6) new smoker (nonsmoker/exsmoker who started during follow-up). Additional adjusting for oral/inhaled respiratory medication was considered in sensitivity analyses.

The risk of each outcome at follow-up was analyzed in separate longitudinal analyses on the appropriate cohort of subjects at risk (Fig 1) defined by excluding prevalent cases at baseline. Incidence rates were estimated, as described elsewhere.[10] The associations of the baseline slope (categorized) and Δslope (standardized continuous covariate) with the outcomes were estimated based on incidence rate ratios (IRRs) computed by using Poisson regression models, with a random-intercept term at level 2 (ECRHS center), follow-up time as an offset, and the previously mentioned potential confounders forced in the models as fixed effects. The statistical interactions of the baseline slope with sex, age, and Δslope were tested by using likelihood ratio tests on appropriate interaction terms. The statistical analyses were performed with STATA software, release 12.1 (StataCorp, College Station, Tex).

RESULTS

Participation in ECRHS I and II

A total of 9748 subjects from 26 centers in 12 countries participated in ECRHS I stage 2 (1991-1993, baseline) and had valid lung function and methacholine challenge test measurements (Fig 1). Of these subjects, 6053 (62%) attended the second

TABLE I. Baseline characteristics of the subjects in the ECRHS I according to their participation in the ECRHS II

Baseline covariates	Participation in ECRHS II			*P* value
	No (n = 3695)	Yes, with spirometry and MCT at follow-up (n = 3851)	Yes, without spirometry and MCT at follow-up (n = 2202)	
Female sex, no. (%)	1785 (48)	1869 (49)	1183 (54)	<.001
Age (y)*	32.8 ± 7.1	33.9 ± 7.1	33.9 ± 7.2	<.001
Height (m)*	1.71 ± 0.10	1.71 ± 0.09	1.71 ± 0.10	.168
BMI (kg/m^2)	23.7 ± 3.8	23.8 ± 3.6	23.7 ± 3.7	.29
Low education, no. (%)	310 (10)	406 (11)	248 (11)	.46
Smoking habits, no. (%)				<.001
Nonsmoker	1387 (38)	1675 (44)	931 (43)	
<15 Pack years	1453 (40)	1464 (39)	796 (37)	
≥15 Pack years	782 (22)	659 (17)	436 (20)	
Sensitization to allergens, no. (%)	1059 (33)	1051 (30)	601 (30)	.010
FEV_1 (% predicted)[24]*	103.6 ± 12.1	104.7 ± 11.8	104.1 ± 12.7	<.001
PD20 (≤1 mg), no. (%)	527 (14)	380 (10)	310 (14)	<.001
Slope (U)*	7.5 ± 2.2	7.9 ± 2.0	7.6 ± 2.2	<.001

MCT, Methacholine challenge test.
*Mean ± SD reported.

survey, and 3851 had complete lung function and methacholine challenge data. On average, the follow-up time was 9 ± 1 years (range, 7-11 years). Women, nonsmokers, and older subjects were more likely to take part in the follow-up than men, ever smokers, and younger subjects (Table I).[24] Subjects who were followed up were less likely to be sensitized to allergens at baseline than subjects who were not followed up. Subjects who had complete lung function and methacholine challenge data had a slightly better lung function (FEV_1 percent predicted[24]) and lower airway responsiveness at baseline.

Degree of airway responsiveness at baseline and its change at follow-up

The mean slope at baseline was 7.9 ± 2.0 (coefficient of variation [CV], 0.3). Subjects with the lowest and highest degree of responsiveness had slopes of 20 to 9.4 and 6.5 to 1.2, respectively (Fig 2). Almost all (n = 373 [98%]) the subjects with PD_{20} values of 1 mg of methacholine or less had the highest degree of responsiveness according to the slope (values, 6.5-1.2; Fig 3). However, among the subjects with PD_{20} values of greater than 1 mg of methacholine, there was a similar number of subjects who had a 6.5 to 1.2 slope (n = 394 [11%]).

The Δslope was 0.02 ± 0.24 (CV, 14.93; 5th-95th percentile, −0.34 to 0.37), which indicates a slight increase in airway responsiveness over time and a very large variability in Δslope across subjects.

Risk of asthma, COPD, and allergic rhinitis at follow-up

The crude incidence rates at follow-up (Table II) ranged between 1.8/1000/y and 13.6/1000/y (lowest to highest airway responsiveness) for asthma, between 1.4/1000/y and 6.2/1000/y for COPD, and between 5.3/1000/y and 11.2/1000/y for allergic rhinitis (all $P_{trend} < .001$). When adjusted for the Δslope and potential confounders (Table III), the risk of asthma was 2- to 3-fold for subjects with a baseline slope ranging between 9.3 and 6.6 (ie, the 3 groups at intermediate responsiveness) with respect to the reference (slope, 20-9.4), whereas the most responsive subjects (slope, 6.5-1.2) had an 11-fold increased risk

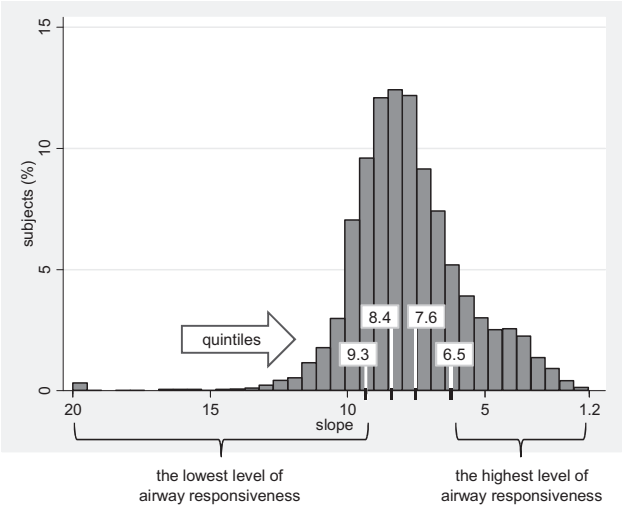

FIG 2. Distribution of the baseline slope, with the quintiles indicated in *boxes*, among the subjects who underwent spirometry and methacholine challenge tests at both surveys (n = 3851).

($P_{trend} < .001$). COPD risk increased significantly as the degree of responsiveness increased ($P_{trend} = .005$), and this increase was statistically significant for subjects with a slope of 8.4 to 7.7 (3-fold increase) and in the most responsive group (6-fold increase). The risk of allergic rhinitis was 2- and 5-fold significantly greater in the 2 most responsive groups, respectively ($P_{trend} < .001$).

Independent of baseline value, an increase in responsiveness at follow-up corresponding to a 1−SD Δslope increment was associated with a 62% and 55% increase in the risk of asthma and allergic rhinitis (both $P < .001$), respectively, whereas Δslope was not associated with COPD. Sex, age, and Δslope did not modify the association between baseline slope and disease risk.

Sensitivity analyses

The main analyses were repeated by using alternative disease definitions, as well as applying different criteria to select the cohorts at risk and analyzing each outcome in subjects who were

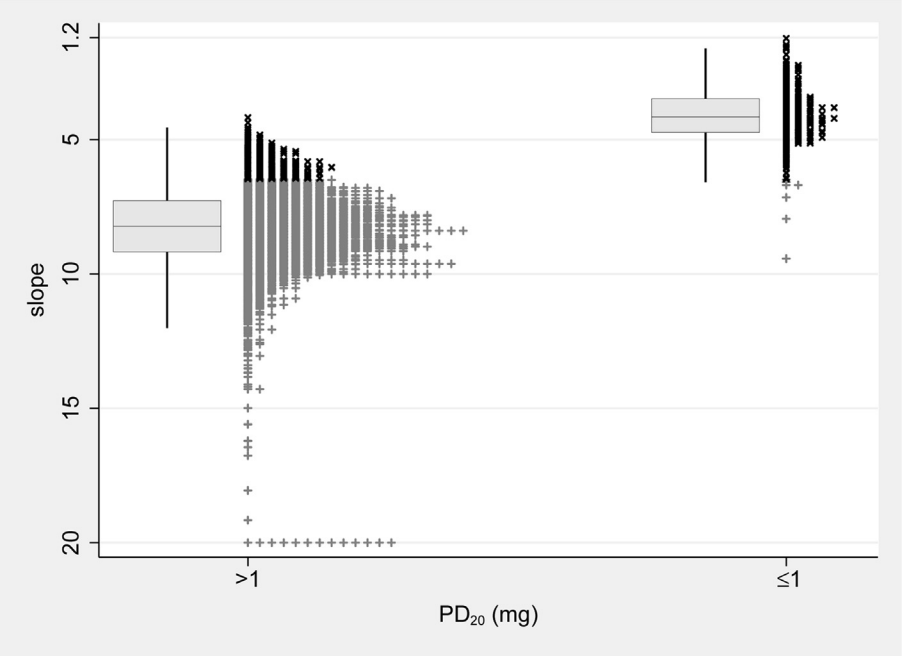

FIG 3. Distribution of the baseline slope in subjects with PD_{20} values of greater than 1 mg of methacholine (n = 3471 [90%]) and 1 mg of methacholine or less (n = 380 [10%]) among the subjects who underwent spirometry and methacholine challenge tests at both surveys (n = 3851). *Boxes* represent the median with interquartile range of the slope distribution, and *whiskers* represent the 1.5 * interquartile range limits. *Black "x" symbols* represent subjects with the highest degree of airway responsiveness (slope, 6.5-1.2); *gray "+" symbols* represent subjects with a lower degree of responsiveness (slope, 20-6.6).

TABLE II. Number of incident cases and crude incidence rates with 95% CIs of new-onset asthma, COPD, and allergic rhinitis at follow-up according to the baseline slope and *P* values for trend across groups

	Crude incidence rates (95% CI),* new cases/1000/y		
	Asthma	**COPD**	**Allergic rhinitis**
Prevalent cases (no.)	258	205	667
Subjects at risk (no.)	3590	3213	3028
Slope			
20-9.4‡	n = 12, 1.8 (0.9-3.2)	n = 9, 1.4 (0.7-2.7)	n = 31, 5.3 (3.7-7.8)
9.3-8.5	n = 30, 4.5 (3.0-6.4)	n = 12, 1.9 (1.0-3.4)	n = 33, 5.7 (4.0-8.1)
8.4-7.7	n = 21, 3.2 (2.0-4.9)	n = 24, 3.9 (2.5-5.8)	n = 29, 5.3 (3.7-7.8)
7.6-6.6	n = 30, 4.7 (3.2-6.7)	n = 14, 2.5 (1.4-4.2)	n = 37, 6.9 (5.0-9.8)
6.5-1.2	n = 76, 13.6 (10.7-17.1)	n = 26, 6.2 (4.0-9.0)	n = 50, 11.2 (8.6-15.3)
P_{trend}†	<.001	<.001	<.001

*Computed on the appropriate cohorts of subjects at risk (Fig 1); exact 95% CIs were computed by using the Poisson distribution.
†Obtained by testing the linear regression coefficient of the slope treated as a continuous covariate.
‡Lowest degree of airway responsiveness.

free from the other 2 diseases investigated (see Tables E1-E3 in this article's Online Repository at www.jacionline.org). These analyses confirmed the main associations observed, with one exception. When asthma risk was studied in subjects who were free from COPD and allergic rhinitis, the association with the baseline slope was weaker, and only the most responsive subjects had a significant excess risk with respect to the least responsive (IRR, 4.03; 95% CI, 1.44-11.25; $P = .008$; see Table E1). When COPD was defined according to the GOLD criterion instead of the LLN, the dose-response relationship between airway responsiveness and COPD was stronger (see Table E2). Additional adjustment for use of respiratory medication did not affect our results, although the association estimates were weakened in the case of asthma (see Table E1).

DISCUSSION

We investigated the association of baseline airway responsiveness and its change over a 9-year follow-up with the risk of asthma, COPD, and allergic rhinitis in a large random sample of young European adults. Methacholine challenge tests were performed in 26 centers according to a standardized protocol, which included the monthly calibration of nebulizer output and identical training for fieldworkers.[3]

TABLE III. IRRs with 95% CIs for the association of the baseline slope and Δslope with the development of asthma, COPD, and allergic rhinitis

	IRR* (95% CI)		
	Asthma (n = 2871)‡	COPD (n = 2573)‡	Allergic rhinitis (n = 2612)‡
Baseline slope			
20-9.4†	1	1	1
9.3-8.5	2.79 (1.32-5.93)	1.85 (0.70-4.86)	1.57 (0.92-2.68)
8.4-7.7	2.40 (1.08-5.33)	2.69 (1.07-6.75)	1.71 (0.96-3.04)
7.6-6.6	3.28 (1.50-7.18)	1.51 (0.51-4.48)	2.50 (1.43-4.36)
6.5-1.2	10.86 (5.09-23.15)	5.68 (2.05-15.73)	5.05 (2.87-8.88)
P_{trend}§	<.001	.005	<.001
Δslope (+1 SD)‖	1.62 (1.33-1.97)	1.15 (0.85-1.57)	1.55 (1.30-1.84)

*Also adjusted for sex, age, height, BMI, FEV_1, education level, and allergen sensitization (not included in the analysis of allergic rhinitis because it was part of the outcome definition) at baseline; season when the methacholine challenge test was performed at baseline and follow-up; moving to a new house and ΔBMI over follow-up; and lifetime smoking habits. Estimates were computed on the appropriate cohort of subjects at risk (Fig 1).

†Lowest degree of airway responsiveness.

‡Number of subjects in the complete case analyses.

§Obtained by testing the linear regression coefficient of the slope treated as a continuous covariate.

‖A positive Δslope value indicates an increase in airway responsiveness at follow-up with respect to baseline.

Our main findings are as follows. First, a greater degree of airway responsiveness at baseline, indicated by a slope of less than the first quintile of its frequency distribution, was consistently associated with a greater risk of asthma, COPD, and allergic rhinitis. Second, an association between baseline slope and disease risk was found, even in subjects who did not reach a 20% decrease in FEV_1 at the maximum cumulative dose of 1 mg of methacholine. Finally, independent of baseline value, an increased degree of airway responsiveness over time predicted a greater risk of asthma and allergic rhinitis.

As for other epidemiologic studies, our investigation had a certain degree of loss to follow-up, especially among young smokers. The subjects included in the analysis had a slightly lower degree of airway responsiveness at baseline than those who were not included. In our view this is more likely to have biased our results toward the null rather than in the opposite direction because less healthy subjects are more prone to refuse or be excluded from methacholine challenge testing than healthy subjects.

The analyses were adjusted for sex, age, BMI; height and FEV_1 as proxies of airway caliber; education as a socioeconomic indicator; allergen sensitization, seasonality; and moving as an indicator of a change in environment; and smoking. Because smoking is strongly related to airway responsiveness, we adjusted for both smoking status and smoking cessation or initiation between the 2 surveys. The use of respiratory medication was also considered in sensitivity analyses, and it did not affect our results.

How to measure airway responsiveness

AHR is associated with several respiratory diseases, including asthma and COPD, and it can reflect either an increased sensitivity to bronchoconstrictors or a more severe response to the stimulus.[25] Several methods and indicators have been developed to measure airway responsiveness,[3,4,6,26] and which one is the best for use in either clinical or epidemiologic practice is still an open question. Although PD_{20} measures the leftward shift of the dose-response curve (airway sensitivity), the slope more strictly relates to the steepness of the descending curve (airway reactivity), and it could better reflect the severity of bronchoconstriction after irritant exposures.[25] The main indicator of responsiveness considered in our study was the transformed dose-response slope, which was calculated according to the method of Chinn et al.[3,4] This indicator was developed to make between-center comparisons possible in multicenter studies, such as the ECRHS, because it is less affected by variation in nebulizer output than PD_{20}.[4] Unlike PD_{20}, the slope is not censored and can be measured for all subjects with at least 2 doses. Chinn et al[22] showed that the short-term repeatability of the slope was at least as good as that of PD_{20}.

Our results document that almost all the subjects with PD_{20} values of 1 mg of methacholine or less (hyperresponsive) at baseline had a slope of less than the first quintile of baseline distribution (the most responsive group, according to this indicator). However, there was about a similar number of subjects with a PD_{20} value of greater than 1 mg of methacholine and a slope of less than the first quintile who shared the same 11-, 6-, and 5-fold increased risk of having asthma, COPD, and allergic rhinitis, respectively, after a 9-year follow-up compared with the reference group. These results were confirmed by all the sensitivity analyses, in which alternative definitions of either the disease or the cohort at risk were applied. Furthermore, our data highlight that there was at least another 20% of the population who, in spite of having lower responsiveness (higher slope) than the previous group, still had a significantly increased risk of the respiratory conditions under investigation and that variation in the slope was associated with wide and statistically significant variation in disease risk, even in subjects with PD_{20} values of greater than 1 mg of methacholine. Overall, these results document that using the slope provides a clear advantage over a dichotomous definition of AHR based on PD_{20}, confirming that airway reactivity is a more sensitive measure of responsiveness with respect to airway sensitivity.[27] These findings encourage the use of a continuous noncensored indicator of airway responsiveness in clinical and epidemiologic practice.

Airway responsiveness and asthma

The predictive value of AHR on asthma in adults is acknowledged.[28,29] In a cohort study on the same ECRHS population, Antó et al[28] found that a PD_{20} value of 1 mg of methacholine or less was associated with a greater than 3-fold increase in asthma risk with respect to a PD_{20} value of greater than 1 mg of methacholine. It is not surprising that our risk estimate (IRR, approximately 11) was much greater than that reported by Antó et al because we compared the most responsive (lowest slope) subgroup of subjects with PD_{20} values of 1 mg of methacholine or less with the least responsive (highest slope) subgroup of subjects with PD_{20} values of greater than 1 mg of methacholine. What our report adds is that the variability in disease risk could be explained by the variability in the slope, even in nonhyperresponsive subjects (ie, with PD_{20} values of greater than 1 mg of methacholine). Interestingly, the asthma incidence rate was 1.8 (95% CI, 0.9-3.2 cases/1000/y) in the least responsive group, which would underline that asthma in non–methacholine-responsive subjects is not completely uncommon, although it is rare.

The definition of asthma based on self-reporting has been previously validated and showed very good agreement with clinical judgment.[30] It seems very unlikely that variations in doctors' diagnostic propensities over time could have biased our results because our findings were confirmed when either a more sensitive definition of asthma at baseline (asthma-like symptoms in the last 12 months) or a more specific disease definition at follow-up (doctor diagnosis) was used.

Airway responsiveness and COPD

A relationship between airway responsiveness and COPD has been reported.[10,29] However, it is still unclear whether airway responsiveness is a risk factor for COPD or whether the early disease initiates the changes that cause increased responsiveness.[31] In our study subjects without asthma with greater responsiveness at baseline were more likely to have COPD at follow-up, and a dose-response relationship between lower slope and greater disease incidence was observed. This would support the hypothesis that airway responsiveness is a risk factor for COPD, but 2 caveats are needed.

First, prebronchodilator spirometric values were only available to define COPD. As a consequence, subjects with asthma with fully or partially reversible obstruction could have been misclassified as having COPD. All subjects who reported lifetime asthma were excluded to minimize this potential bias. This approach is generally used to investigate COPD when results of postbronchodilator spirometry are not available.[29,32] It was shown that this definition of COPD identifies a group of subjects with a greater lung function decrease and hospitalization rate than the healthy population.[33] Moreover, when the main analyses were restricted to the subgroup of subjects who did not even report asthma-like symptoms, the COPD risk estimates obtained were even greater. Thus in our view it is extremely unlikely that asthma/COPD misclassification could have seriously biased our results.

The second caveat relates to the fact that there is still no consensus on the best definition of COPD.[10,34,35] In our study COPD was defined as an FEV_1/FVC ratio of less than the fifth percentile of the distribution in a healthy reference population, as recommended by the European Respiratory Society Task force for epidemiologic studies on COPD.[36] When COPD was alternatively defined according to the GOLD fixed-cutoff criterion,[23] the dose-response relationship between airway responsiveness and COPD risk was even stronger. Although confirmatory studies with postbronchodilator spirometry are needed, these findings support the hypothesis that airway responsiveness is not merely a marker of airflow obstruction but also a risk factor for COPD, and they are in line with the observation that airway responsiveness reflects the inflammatory process underlying COPD.[37]

Airway responsiveness and allergic rhinitis

A cross-sectional association between AHR and allergic rhinitis has been reported in several studies,[38,39] but it is still uncertain whether they are causally linked. A previous study by Shaaban et al[12] based on the ECRHS showed that, among subjects with neither asthma nor AHR (as indicated by PD_{20} values of 1 mg of methacholine or less), subjects with allergic rhinitis were more likely to have AHR at follow-up than those without. The authors also stated that the opposite association (ie, AHR preceding rhinitis) was not supported.[12] When we repeated the analyses by Shaaban et al on the same population (ie, excluding subjects with asthma; data not shown), we arrived at the same conclusion. However, when we also used the slope instead of the PD_{20} dichotomous indicator, we could still observe a clear dose-response relationship between responsiveness (the slope) and disease risk (see Table E3). In conclusion, the apparent inconsistency between our study and that of Shaaban et al can be explained by the greater sensitivity of the slope to detect variations in disease risk with respect to PD_{20}.

The lack of a unidirectional association between airway responsiveness and allergic rhinitis could support the hypothesis that both conditions are the expression of a common pathophysiologic process. Chronic inflammation of the airways is actually involved in both conditions, and some researchers have proposed the upper and lower airways to be part of a single united compartment.[39,40] Furthermore, airway responsiveness and allergic rhinitis seem to share some genetic determinants.[41]

Change in degree of airway responsiveness over time

Airway responsiveness is known to change over time in the same subject.[13,14] This was confirmed in our data because the variability of the Δslope was much greater than that of the baseline slope (CVs, 14.93 and 0.3, respectively). Independent of baseline value, the Δslope was a strong predictor of both new-onset asthma and allergic rhinitis: a 1−SD Δslope increment was associated with a 62% and 55% increased disease risk, respectively, whereas the association with COPD risk was less consistent across different analyses. These findings would suggest that monitoring changes in responsiveness over time can be clinically significant. However, they must be interpreted cautiously because both the disease and change of responsiveness were assessed simultaneously during the follow-up examination, and one could argue that increased responsiveness could itself be an expression of disease.

Further sensitivity analyses

Asthma, COPD, and allergic rhinitis have a considerable overlap, and they frequently coexist.[42,43] In the young adult population COPD is uncommon, and there might be a diagnostic propensity for asthma (instead of COPD) in patients with non–fully reversible airflow obstruction. For these reasons, sensitivity analyses were performed on subjects who were free of the other 2 diseases both at baseline and follow-up for each outcome. All in all, these analyses confirmed the main results of the study, even if in the case of asthma the associations were weakened, apparently because of a loss of statistical power (approximately 800 subjects less). These analyses would support the fact that misclassification caused by overlapping conditions or confounding caused by common risk factors are unlikely explanations of the associations observed.

In summary, we found a dose-response relationship between airway responsiveness and the development of asthma, COPD, and allergic rhinitis, even in subjects who did not reach a 20% decrease in FEV_1 at the cumulative dose of 1 mg of methacholine. This finding supports the use of a continuous noncensored indicator of responsiveness like the slope at least in epidemiologic studies because the clinical importance of low degrees of responsiveness is likely to be underestimated when using the dichotomized PD_{20}. Understanding the mechanisms underlying airway responsiveness can be very helpful for the development of

effective drugs because airway responsiveness is involved in several respiratory diseases. Although bronchial challenge tests are unlikely to be cost-effective as screening tests in the general population, changes in responsiveness over time could play an important prognostic role for subjects with respiratory symptoms or established disease.

Clinical implications: A continuous noncensored indicator of airway responsiveness, such as the slope of the methacholine dose-response curve, shows clinical advantages over PD_{20}. Monitoring changes in responsiveness over time could be clinically relevant.

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METHODS

Sensitivity analyses

The main analysis of asthma risk was repeated:

1. excluding the subject who had reported asthma-like symptoms (wheezing or whistling without a cold or having been woken by an attack of shortness of breath in the past 12 months)[E1] at baseline;
2. defining incident asthma as a positive answer to the questions "Have you ever had asthma?" and "Was this confirmed by a doctor?" at follow-up (but not at baseline);
3. excluding the subjects who had an FEV_1/FVC ratio of less than LLN or allergic rhinitis either at baseline or follow-up; and
4. adjusting for use of oral/inhaled respiratory medication in the last 12 months at baseline and follow-up.

The main analysis of COPD risk was repeated:

1. excluding the subjects who had reported asthma-like symptoms either at baseline or follow-up;
2. defining incident COPD as a prebronchodilator FEV_1/FVC ratio of less than 0.70, according to the GOLD guidelines,[E2] at follow-up (but not at baseline);
3. excluding the subjects who had reported allergic rhinitis either at baseline or at follow-up; and
4. adjusting for use of oral/inhaled respiratory medication in the last 12 months at baseline and follow-up.

The main analysis of allergic rhinitis risk was repeated:

1. excluding the subjects who had asthma either at baseline or follow-up, as in the sensitivity analysis by Shaaban et al[E3];
2. excluding the subjects who had asthma or a FEV_1/FVC ratio of less than LLN either at baseline or follow-up; and
3. adjusting for use of oral/inhaled respiratory medication in the last 12 months at baseline and follow-up.

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TABLE E1. IRRs with 95% CIs for the association of baseline slope and Δslope with the development of new-onset asthma

	IRR* (95% CI)				
	Main analysis	**Sensitivity analysis 1, excluding subjects who reported asthma-like symptoms‡ at baseline**	**Sensitivity analysis 2, defining incident asthma as a positive answer to both "Have you ever had asthma?" and "Was this confirmed by a doctor?"**	**Sensitivity analysis 3, excluding subjects who had allergic rhinitis or FEV_1/FVC ratios of less than LLN either at baseline or follow-up**	**Sensitivity analysis 4, adjusting for use of oral/inhaled respiratory medication in the last 12 mo at baseline and follow-up**
No. of subjects at risk (complete case analysis)	2871	2571	2870	2041	2820
Baseline slope					
20-9.4†	1	1	1	1	1
9.3-8.5	2.79 (1.32-5.93)	2.29 (1.05-4.98)	2.50 (1.12-5.56)	1.73 (0.66-4.48)	1.81 (0.85-3.86)
8.4-7.7	2.40 (1.08-5.33)	2.16 (0.96-4.87)	2.33 (1.01-5.40)	1.66 (0.61-4.48)	1.63 (0.73-3.65)
7.6-6.6	3.28 (1.50-7.18)	2.52 (1.11-5.71)	2.78 (1.20-6.43)	1.98 (0.72-5.43)	2.21 (1.01-4.81)
6.5-1.2	10.86 (5.09-23.15)	6.72 (3.02-14.97)	10.49 (4.72-23.35)	4.03 (1.44-11.25)	5.10 (2.38-10.92)
Δslope (+1 SD)§	1.62 (1.33-1.97)	1.53 (1.22-1.92)	1.60 (1.30-1.99)	1.37 (1.00-1.87)	1.41 (1.15-1.72)

*Also adjusted for sex, age, height, BMI, FEV_1, education level, and allergen sensitization at baseline; season when the methacholine challenge test was performed at baseline and follow-up; moving to a new house and ΔBMI over follow-up; and lifetime smoking habits.

†Lowest degree of airway responsiveness.

‡Wheezing or whistling without a cold or having been woken by an attack of shortness of breath in the past 12 months.

§A positive Δslope value indicates an increase in airway responsiveness at follow-up with respect to baseline.

TABLE E2. IRRs with 95% CIs for the association of baseline slope and Δslope with the development of new-onset COPD

	IRR* (95% CI)				
	Main analysis	Sensitivity analysis 1, excluding subjects who had reported asthma-like symptoms‡ either at baseline or follow-up	Sensitivity analysis 2, defining COPD as prebronchodilator FEV_1/FVC ratio <0.70[E2] at follow-up (but not at baseline)	Sensitivity analysis 3, excluding subjects who had reported allergic rhinitis either at baseline or follow-up	Sensitivity analysis 4, adjusting for use of oral/inhaled respiratory medication in the last 12 mo at baseline and follow-up
No. of subjects at risk (complete case analysis)	2573	2154	2679	2035	2555
Baseline slope					
20-9.4†	1	1	1	1	1
9.3-8.5	1.85 (0.70-4.86)	1.58 (0.48-5.15)	2.65 (0.75-9.34)	2.17 (0.72-6.57)	1.86 (0.71-4.88)
8.4-7.7	2.69 (1.07-6.75)	2.57 (0.86-7.68)	3.58 (1.06-12.10)	3.51 (1.22-10.08)	2.71 (1.08-6.81)
7.6-6.6	1.51 (0.51-4.48)	1.52 (0.43-5.43)	7.15 (2.13-24.01)	1.81 (0.51-6.49)	1.53 (0.51-4.55)
6.5-1.2	5.68 (2.05-15.73)	6.89 (2.11-22.49)	9.91 (2.71-36.30)	6.09 (1.82-20.31)	5.75 (2.08-15.91)
Δslope (+1 SD)§	1.15 (0.85-1.57)	1.08 (0.75-1.55)	1.53 (1.09-2.16)	1.15 (0.80-1.66)	1.15 (0.84-1.56)

*Also adjusted for sex, age, height, BMI, FEV_1, education level, and allergen sensitization at baseline; season when the methacholine challenge test was performed at baseline and follow-up; moving to a new house and ΔBMI over follow-up; and lifetime smoking habits.

†Lowest degree of airway responsiveness.

‡Wheezing or whistling without a cold or having been woken by an attack of shortness of breath in the past 12 months.

§A positive Δslope value indicates an increase in airway responsiveness at follow-up with respect to baseline.

TABLE E3. IRRs with 95% CIs for the association of baseline slope and Δslope with the development of new-onset allergic rhinitis

	IRR* (95%CI)			
	Main analysis	**Sensitivity analysis 1, excluding subjects who had asthma either at baseline or follow-up§**	**Sensitivity analysis 2, excluding subjects who had asthma or FEV_1/FVC ratio less than LLN either at baseline or follow-up**	**Sensitivity analysis 3, adjusting for use of oral/inhaled respiratory medication in the last 12 mo at baseline and follow-up**
No. of subjects at risk (complete case analysis)	2612	2434	2237	2597
Baseline slope				
20-9.4†	1	1	1	1
9.3-8.5	1.57 (0.92-2.68)	1.35 (0.77-2.35)	1.27 (0.72-2.24)	1.44 (0.84-2.48)
8.4-7.7	1.71 (0.96-3.04)	1.38 (0.76-2.53)	1.38 (0.75-2.55)	1.64 (0.92-2.91)
7.6-6.6	2.50 (1.43-4.36)	2.07 (1.15-3.73)	2.16 (1.19-3.92)	2.34 (1.35-4.07)
6.5-1.2	5.05 (2.87-8.88)	3.46 (1.85-6.50)	3.74 (1.94-7.21)	4.43 (2.51-7.82)
Δslope (+1 SD)‡	1.55 (1.30-1.84)	1.49 (1.23-1.80)	1.51 (1.24-1.83)	1.51 (1.27-1.79)

*Also adjusted for sex, age, height, BMI, FEV_1, and education level at baseline; season when the methacholine challenge test was performed at baseline and follow-up; moving to a new house and ΔBMI over follow-up; and lifetime smoking habits.

†Lowest degree of airway responsiveness.

‡A positive Δslope value indicates an increase in airway responsiveness at follow-up with respect to baseline.

§Population considered by Shaaban et al.[E3]