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Title

Asthma, COPD, and overlap syndrome: a longitudinal study in young European adults

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Authors' contributions to the study

RdM and AM conceived the idea for this paper, planned and performed the statistical analysis, and drafted the manuscript. All the authors participated in discussing the study design, the definitions of the outcomes and covariates, they revised and made substantial contributions to the manuscript. All the authors have seen and approved the final version of the manuscript.

Running title

Asthma-COPD overlap syndrome in young adults

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COMPETING INTERESTS

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ABSTRACT

Background: We compared risk factors and clinical characteristics, 9-year lung function change and hospitalization risk, across subjects with the asthma-COPD overlap syndrome (ACOS), asthma or COPD alone, or none of these diseases.

Methods: Participants in the European Community Respiratory Health Survey in 1991-1993 (age 20-44 years) and 1999-2001 were included. Chronic airflow obstruction was defined as pre-bronchodilator FEV1/FVC<lower limit of normal on both occasions. Based on their history of respiratory symptoms, spirometry and risk factors, subjects were classified as having: asthma alone (n=941), COPD alone (n=166), ACOS (n=218) and none of these (n=5,659).

Results: Subjects with ACOS shared risk factors and clinical characteristics with subjects with asthma alone, whereas they had an earlier age at asthma onset. FEV1 change in the ACOS group (-25.9 mL/yr) was similar to that in the asthma group (-25.3 mL/yr), and lower ($p<0.001$) than in the COPD group (-37.3 mL/yr). ACOS was associated with the highest hospitalization rate.

Conclusion: Among young adults aged 20-44 years, ACOS seems to represent a form of severe asthma, characterized by more frequent hospitalizations, and to be the result of early-onset asthma that has progressed to fixed airflow obstruction.

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Abbreviations:

ACOS, asthma-COPD overlap syndrome

AHR, airway hyperresponsiveness

BMI, body mass index

COPD, chronic obstructive pulmonary disease

ECRHS, European Community Respiratory Health Survey

ER, emergency room

ETS, environmental tobacco smoke

FEV1, forced expiratory volume in 1 s

FVC, forced vital capacity

LLN, lower limit of normal

"Take home" message:

The asthma-COPD overlap syndrome in young adults is a form of early-onset severe asthma with recurrent exacerbations

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are a major public health problem, and they co-exist in a large proportion of subjects.[1-6] Patients with the asthma-COPD overlap syndrome (ACOS) have a more rapid disease progression, more respiratory symptoms, exacerbations, co-morbidities and health care utilization, as compared to subjects with either disease alone.[7-10]

According to some authors, ACOS is a syndrome in which older adults, generally with a significant history of smoking, have a partially reversible or fixed airflow obstruction and evidence of atopy or asthma.[11] It is still an open question whether ACOS is the result of asthma that has progressed to fixed airflow obstruction, or the expression of COPD in patients with airway hyperresponsiveness (AHR), or a specific disease entity.[12, 13]

Few epidemiological studies have investigated the joint epidemiological distribution of asthma and COPD in the general population, as well as the long-term outcomes of ACOS.[5, 11, 14] Indeed, ACOS is often an exclusion criterion in studies investigating asthma or COPD.[9, 15]

The aims of this prospective study were to assess, in an international cohort of young adults from the general population participating in the European Community Respiratory Health Survey (ECRHS), whether clinical characteristics and risk factors, long-term lung function decline and risk of being admitted to hospital or Emergency Room (ER) vary among subjects with asthma, COPD and ACOS.

METHODS

Study design

The ECRHS I was an international multicentre study performed between 1991 and 1993 on random samples of young adults (20–44 yr) from the general population (www.ecrhs.org).[16] From those who responded to a screening questionnaire (stage 1), a 20% "random sample" and an additional ''symptomatic sample'' (subjects with recent asthma-like symptoms or use of asthma medication) were selected for a clinical examination (stage 2), which is called the "baseline" examination from now on. All participants in stage 2 were invited to take part in the "follow-up" examination (ECRHS II) between 1999 and 2002.[17] Ethical approval was obtained for each centre from institutional or regional ethics committees and written consent was obtained from the participants.

The maximum pre-bronchodilator FEV1 and FVC were measured at both surveys.[18] *Chronic airflow obstruction* was defined as a pre-bronchodilator FEV1/FVC< lower limit of normal (LLN) both at baseline and at follow-up.[19] *Transient airflow obstruction* was defined as a FEV1/FVC<LLN at baseline but not at follow-up. Predicted lung function values were computed.[20] Airway hyperresponsiveness (AHR) was defined as a FEV1 decrease of 20% after a cumulative methacholine dose ≤1 mg. Allergen sensitization was present if levels of serum immunoglobulin E for house dust mite, cat dander, timothy grass, or Cladosporium species were >0.35 kU/L. Body height and weight were measured and body mass index (BMI) was computed (kg/m^2).

Definitions

At baseline, a subject was considered to have *current asthma* if:

1) she/he reported to have or have had asthma AND one among:

- asthma-like symptoms (wheezing/whistling in the chest; chest tightness; shortness of breath at rest/following strenuous activity/at nighttime; asthma attacks)
- use of inhaled/oral medicines for breathing problems in the last year
- AHR
- transient airflow obstruction.

OR

2) she/he reported asthma-like symptoms in the last year AND she/he had AHR.

Since post-bronchodilator spirometry was not performed in ECRHS I and II, a subject was considered to have *COPD* at baseline if she/he had pre-bronchodilator chronic airflow obstruction AND one among:

- symptoms (shortness of breath after strenuous activity, or dyspnoea [trouble with breathing], or chronic bronchitis [having cough or phlegm on most days for as long as three months each year for ≥2 years])
- a history of active smoking (≥10 pack-years),[21] or occupational exposure to vapours, dust, gas or fumes (indicated by a positive answer to "Have you ever worked in a job which exposed you to vapors, gas, dust or fumes?").

The validity of our definition of pre-bronchodilator chronic airflow obstruction was assessed using preliminary post-bronchodilator lung function data collected in ECRHS III (2010-2014). The findings (see section 1 of the online supplementary material) suggest that "chronic airflow obstruction" is a valid measurement of fixed airflow obstruction (sensitivity = 80.2%, specificity = 98.3%), and that the rate of misclassification is very similar for subjects with and without asthma (positive predictive value = 73.9% and 69.3%, respectively).

Finally, subjects were classified into four mutually exclusive groups at baseline:[5] 1) "*healthy*" *subjects* (neither current asthma nor COPD); 2) *current asthma alone* (asthma without COPD); 3) *ACOS* (both current asthma and COPD); 3) *COPD alone* (COPD without asthma).

A similar classification was applied at follow-up to evaluate whether the disease status was stable over the study period (see section 2 of the online supplementary material).

The longitudinal outcomes were:

- absolute FEV1 (and FVC) change over follow-up [(value $_{\text{follow-up}}$ − value $_{\text{baseline}}$) / follow-up time] (mL/year); and FEV1 (and FVC) change as a percentage of baseline value [100 x (value $_{\text{follow-up}}$ − value $_{\text{baseline}}$) / (value $_{\text{baseline}}$ x follow-up time)] (%/year). Negative values represent decline.
- risk (%) of hospitalizations and/or Emergency Room (ER) visits because of breathing problems over follow-up.

Statistical analysis

Prevalence of risk factors and clinical characteristics at baseline (as defined in Tables 2 and 3, also see section 3 of the online supplementary material) were adjusted for sex and age (continuous variable) by logistic regression. Multiple linear and logistic regression models were fitted to data using lung function change and hospitalization rates as dependent variables, respectively, and disease status as the main independent variable. Adjustment variables were age, height, BMI (treated as continuous variables), sex, education, occupational exposure at baseline; lifetime smoking exposure and BMI change over time. All models included a random intercept for ECRHS centres and type of sample (random vs. symptomatic).[22] Missing values were deleted listwise. The statistical analyses were performed using STATA 13.1 (StataCorp, College Station, TX).

In sensitivity analyses:

a) asthma was defined as a positive answer to “have you ever had asthma?” (self-reported asthma) at baseline and COPD was defined as the presence of chronic airflow obstruction (disregarding the presence of symptoms and exposures).
b) ECRHS centres were set as a random intercept and type of sample was set as a fixed effect.

RESULTS

A total of 18,356 subjects from 29 centres in 14 countries participated in the ECRHS I stage 2 (1991–1993: baseline), of whom 15,716 (86%) were from the random sample (Figure 1). Overall, 10,933 (60%) subjects attended the second survey, of whom 9,175 (84%) were from the random sample. Subjects participating in ECRHS II were older, less likely to have ever smoked and had better lung function at baseline than subjects who did not (Table S4 in the Supporting information). Mean follow-up time was 9±1 (range: 4–12) years. Among participants in the second survey who had data on lung function and asthma, 5,659 "healthy" subjects, 941 subjects with current asthma alone, 218 subjects with ACOS, and 166 subjects with COPD alone were identified, while 131 subjects could not be classified (see note of Figure 1). The distribution of subjects across the different sub-definitions of current asthma and COPD is reported in the online supplementary material (Table S5).

Among participants in ECRHS II, the characteristics of the subjects included and not included in the analyses were similar, with the exception that the latter were slightly younger and more likely to have AHR (Table 1). The disease status was relatively stable over time (Table S3): the percentage of subjects that were classified, both at baseline and at follow-up, in the same disease group ranged between 75.7% (COPD alone) and 93.0% (healthy subjects).

Baseline characteristics and risk factors

Subjects with current asthma alone were younger (33.6±7.2 years on average) and more likely to be women than subjects in the other groups (Table 2), while subjects with COPD were the oldest (36.0±6.5 years). Smoking was more frequent among subjects with ACOS or COPD. Among lifetime smokers, the prevalence of heavy smoking (≥15 pack-years) was 51.5% for subjects with COPD alone (median [IQR]: 16.8 [15.9] pack-years), and it ranged from 27.1 (healthy, 9.8 [13.8] pack-years) to 35.1% (ACOS, 10.3 [20.1] pack-years) in the other groups ($p<0.001$). Occupational

exposures were reported more frequently in the COPD (57.4%) and asthma (45.9%) groups than in the reference category (42.0%) (p=0.001). Family asthma and childhood respiratory infections were the most frequent in subjects with asthma or ACOS (p<0.001).

Information on asthma onset was available for 705 (74.9%) subjects with asthma alone and 170 (78.0%) with ACOS. On average, subjects with ACOS had an earlier age of onset (14.9 vs 17.2 years; p=0.016), a longer disease duration (27.7 vs 24.8 years; p=0.003), a greater percentage of inhaled corticosteroid use (30.2 vs 20.6%; p=0.003) and more frequent asthma attacks in the last year (11.2 vs 6.2; p=0.034).

The prevalence rates of wheezing, dyspnoea, chronic bronchitis, allergic rhinitis, eczema, allergen sensitization, as well as the use of medicines and hospital/ER admissions, were the highest for subjects with ACOS or current asthma alone (all p<0.001) (Table 3). The prevalence of AHR ranged from 3.5% (healthy) to 92.1% (ACOS) (p<0.001). Subjects with FEV1 <80% predicted were 4.5% for current asthma alone, 16.4% for COPD alone and 33.1% for the ACOS group (p<0.001).

Change in lung function and risk of hospitalization

Mean change in FEV1 and hospitalization rates at the follow-up are reported in Table 4. After adjusting for potential confounders (Table 5), subjects with COPD alone had a -7.64 (95%CI: -12.6; -2.66) mL/year greater change in FEV1 compared to healthy subjects (p=0.007), whereas their FVC change was -13.83 (95%CI: -19.96; -7.70) mL/year greater (<0.001). Lung function change was similar in asthma, ACOS and healthy subjects. Similar results were obtained when analysing change in lung function as a percentage of baseline value. Subjects with COPD alone, asthma alone, and ACOS, had a 2-fold, 4-fold, and 5-fold greater risk of reporting hospital/ER admissions over the follow-up, with respect to the reference group, respectively (p=0.080).

Sensitivity analyses

When the disease groups were identified according to alternative definitions of asthma (self-reported asthma at baseline) and COPD (chronic obstruction), the distribution of risk factors and clinical characteristics were similar (Tables S6 and S7 in the online supplementary material), with the exceptions that the difference in smoking exposure between subjects with ACOS and healthy subjects, as well as the difference in occupational exposures between subjects with COPD and healthy subjects, shifted to the null. The results of the analyses on lung function change and hospitalization risk were fully confirmed both using these alternative definitions (Table S8), and using an alternative hierarchical model structure (data not shown).

DISCUSSION

The aim of this paper was to better understand the ACOS by investigating its similarities and differences with respect to asthma and COPD alone. This is one of the first studies investigating ACOS in an international population-based cohort. We studied young adults in an age range when disease evolution is still only minimally masked by the effects of cumulative exposure to risk factors and comorbidities.[23] We found that subjects with both asthma and COPD shared with asthmatic subjects risk factors and clinical characteristics, and had a 9-year lung function decline similar to subjects with asthma, significantly lower than in COPD.

Clinical characteristics and risk factors

Previous reports showing that subjects with ACOS have a pattern of risk factors that is intermediate between asthma and COPD, but more exacerbations and greater severity than subjects with either disease alone,[7, 24] raised the hypothesis that ACOS could be a specific disease entity.[12, 13, 25]

As far as we know, studies on ACOS were usually cross-sectional and based on selected groups of elderly patients or medical record data, and collected limited clinical information.[8-10] It is therefore not surprising that our findings are only in partial agreement with previous evidence, as they point out that subjects with ACOS have the same clinical profile and risk factors as asthmatics (even if they represent a more severe subgroup), which was quite different from that of subjects with COPD. Indeed they shared the same prevalence of allergen sensitization, allergic rhinitis and eczema with asthmatics. Almost all of them (92.1%) had AHR. Furthermore they had the same increased prevalence of family asthma history and childhood respiratory infections.[26] Like asthmatics, subjects with ACOS had a greater prevalence of respiratory symptoms, use of medicines and hospital/ER admissions than young COPD patients. With respect to other asthmatics, subjects

with ACOS had an earlier onset and a longer duration of asthma, a higher frequency of smoking and a higher prevalence of males.

In agreement with previous studies on the general population,[27] and in contrast with clinical studies on older patients,[9] we found that subjects with ACOS had worse lung function at baseline than subjects with asthma or COPD alone. With respect to other asthmatics, this result may reflect airway remodelling or a failure to attain maximal airway growth because of an early disease onset,[23] or both. Indeed, a correlation between disease duration and airway remodelling has been reported.[28] The poorer lung function with respect to COPD is probably due to the fact that the effect of the exposures that lead to COPD can only be recognized at older ages.[29]

In the main analyses, definitions of active asthma and COPD were adopted by using information on current symptoms or exposures. For this reason, the distribution of some symptoms and risk factors may have depended on the definitions used. However, when we adopted alternative definitions of asthma and COPD that did not consider the presence of symptoms and risk factors, the distribution of characteristics across disease groups was very similar, with a few exceptions regarding smoking and occupational exposures. In a joint statement of GINA and GOLD,[2] ACOS is defined as "persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD". Accordingly, ACOS was defined as the overlap between asthma and COPD in our study. Thus, it is worth noting that different distributions of characteristics in ACOS vs. asthma (or ACOS vs. COPD) did not depend on the definitions used, but they reflected peculiarities of ACOS as compared to asthma or COPD alone.

Change in lung function and risk of hospitalization

While COPD is characterized by an accelerated, although variable FEV1 decline,[21] many asthmatic patients experience a slow decline.[30] Accordingly, our findings document that subjects with asthma alone had a 9-year decline in lung function that was not different from that of people

without respiratory diseases. Subjects with ACOS, who had the poorest FEV1 and FVC at baseline, had a similar FEV1 and FVC decline to subjects with asthma, but a significantly lower decline than in COPD. One explanation is that the mechanisms and pathways of airflow obstruction in ACOS and COPD may be different. In the ACOS group, they may be due to acquired deficits in lung growth very early in life,[26] while in COPD they are mainly due to a steeper decline in adult life because of risk factor exposure. The younger age at asthma onset in subjects with ACOS in our study is consistent with this hypothesis. The very high prevalence of AHR in ACOS also fits this picture. In fact, AHR is associated with COPD and worse lung function, even when AHR is measured extremely early in life.[31, 32]. Alternatively, subjects with ACOS may have had a severe insult or more frequent exacerbations early in life, which may have caused a significant impairment in lung function that is no longer progressive. However, this might be at least in part due to the efficacy of treatments in preventing lung function deterioration in asthma.[33] To our knowledge, there are only two other longitudinal studies comparing lung function decline of subjects with ACOS, asthma and COPD.[8, 34] Both are clinical studies on older patients and used different disease definitions compared to our study, and the samples investigated were smaller and not representative of the vast majority of cases in the general population. Results from the most recent of these two studies support our conclusion,[34] while the other found that lung function decline in ACOS patients was more similar to that of COPD patients, and greater than in asthma patients.[8]

In agreement with previous clinical studies,[10, 26, 35] our population study showed that ACOS subjects, who had the lowest FEV1 % predicted at baseline, had a rate of hospital/ER admissions for breathing problems during the follow-up that was more than double with respect to subjects with either disease alone. Indeed, asthma with fixed airflow obstruction is one of the main clinical phenotypes of uncontrolled severe asthma,[36] characterized by a poor prognosis and recurrent exacerbations, and reduced FEV1 is an important risk factor for multiple exacerbations both in asthma and COPD.[37]

Study limitations

Like in many other large-scale surveys started in the nineties, post-bronchodilator spirometry was not available. As a consequence, some asthmatic subjects with fully reversible obstruction could have been falsely classified as COPD. To minimize this bias, we used chronic airflow obstruction (pre-bronchodilator FEV/FVC< LLN in both studies, nine years apart) as a spirometric criterion of COPD. A pilot evaluation, based on preliminary post-bronchodilator lung function data of ECRHS III (2010-2014), supports the validity of pre-bronchodilator chronic airflow obstruction as an indicator of fixed obstruction. In fact, sensitivity and specificity were 76.7 and 98.8%, respectively, in subjects without asthma, and 86.4 and 94.3%, respectively, in subjects with asthma (Table S1 in the online supplementary material). This supports the fact that our definition of chronic airflow obstruction captured the majority of subjects with "true" post-bronchodilator obstruction, and that it excluded virtually all subjects without. Moreover, high and fairly similar positive predictive values for subjects with (73.9%) and without (69.3%) asthma suggest non-differential misclassification, strengthening the validity of comparisons between subjects with ACOS and subjects with COPD alone.

Either respiratory symptoms and/or active smoking/occupational exposures were necessary, in combination with the spirometrical criterion, to define COPD.[2, 21] This resulted in a more specific definition as compared to the definition based on spirometry alone.[38] Longitudinal studies with post-bronchodilator lung function data will be needed to adequately compare the level and severity of airflow obstruction in subjects with ACOS and COPD.

Since the study aim was not to estimate disease prevalence in the population but to compare characteristics across disease groups, this analysis included both a random subsample of respondents and all the subjects who reported symptoms suggestive of asthma at the screening questionnaire. As a consequence of the random sampling of the population participating at ECRHS

stage 1, however, the subjects from the disease groups investigated are representative of the disease in the population.

Unfortunately information on inflammatory markers to characterize the ACOS phenotypes was not available in our study.[13] Finally, the participation rate was not particularly high. However, the comparison of baseline information between subjects who did and did not participate showed that the two groups were similar.

Conclusion

Our findings suggest that, at least among young adults aged 20-44 years, the asthma-COPD overlap syndrome represents a form of severe asthma, characterized by more frequent exacerbations, and it is likely to be the result of early asthma that has progressed to fixed airflow obstruction, possibly because of airway remodelling.

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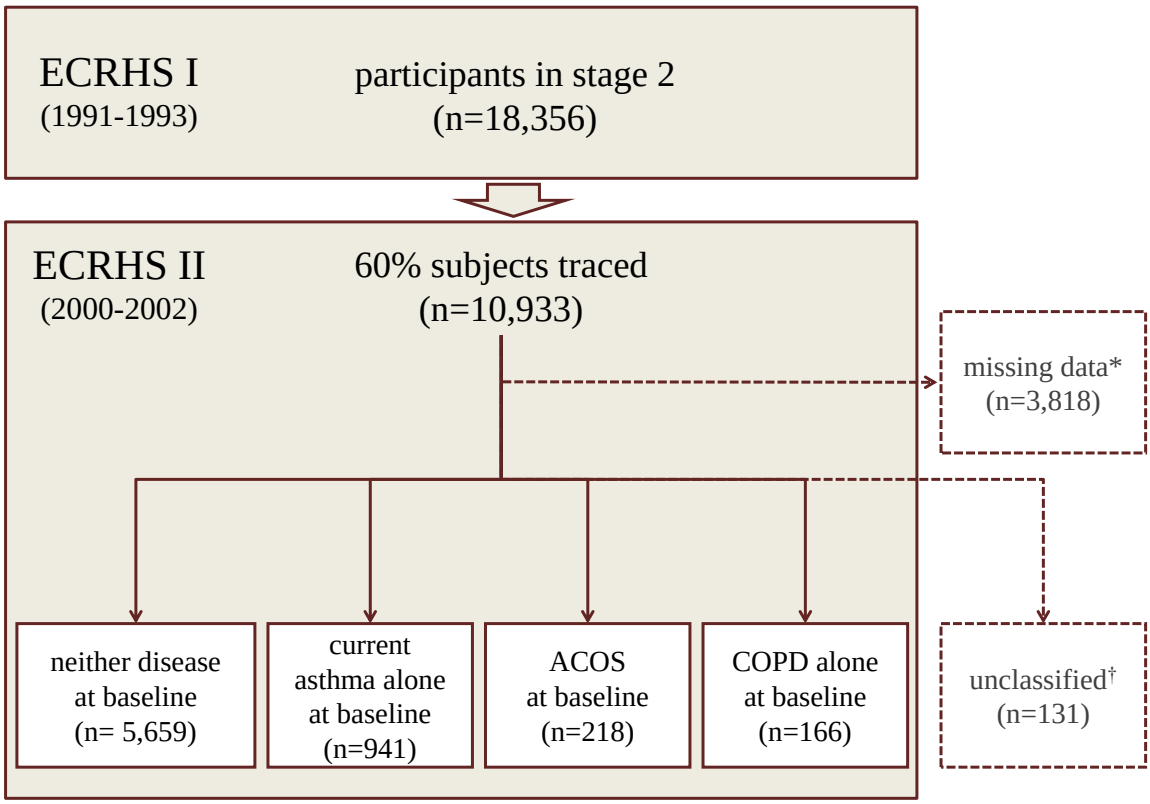
FIGURE LEGENDS

Figure 1: Number of subjects included in the analyses.



ACOS, asthma-COPD overlap syndrome

* for 3,810 subjects spirometry was not available either at baseline and/or follow-up, and 8 subjects did not answer the question on asthma at baseline

† subjects who reported asthma at baseline but did not fulfil the criteria for current asthma (n=67), and subjects who had chronic airflow obstruction but did not fulfil the criteria for COPD (n=64), were not considered in the main analysis

TABLES

Table 1: Baseline (ECRHS I) characteristics of the subjects participating in ECRHS II.

	Subjects included in the analyses (n= 6,984)	**Subjects not included in the analyses** (n= 3,949)	**p-value**
Female gender (n, %)	3,708 (53)	2,100 (53)	0.93
Age (yr)*	34.3 (7.1)	33.7 (7.2)	<0.001
BMI (kg/m^2)*	24.1 (4.0)	24.1 (4.0)	0.53
Low education (n, %)	875 (13)	499 (13)	0.83
Smoking habits (n, %)			
non-smoker	3,067 (45)	1,793 (46)	0.16
< 15 pack-years	2,499 (36)	1,347 (35)	
≥ 15 pack- years	1,321 (19)	722 (19)	
Sensitization to allergens (n, %)	2,130 (34)	970 (35)	0.49
FEV1 % predicted*	105.0 (13.5)	105.0 (15.2)	0.95
AHR (n, %)	886 (15)	398 (18)	0.001

* mean ± SD reported

Table 2. Sex- and age- adjusted prevalence rates with 95%CIs of socio-demographic characteristics, environmental exposures and risk factors at baseline.†

	Healthy (n=5,659)	**Asthma alone** (n=941)	**ACOS** (n=218)	**COPD alone** (n=166)	**overall p-value‡**
Female gender (%)	52.2 (50.8-53.6)	61.2 (58.0-64.3)***	47.7 (41.0-54.3)	47.5 (39.9-55.2)	<0.001
Age (>35 y) (%)	50.8 (47.8-53.7)	44.2 (40.1-48.2)**	50.5 (43.2-57.7)	60.4 (52.5-68.3)*	<0.001
Low education (%)	6.7 (3.7-9.8)	7.4 (3.8-11.0)	7.9 (3.3-12.5)	7.0 (2.4-11.7)	0.80
Lifetime smoker (>0 vs. 0 pack-years smoked) (%)	55.1 (52.6-57.7)	56.5 (52.6-60.3)	64.1 (57.3-70.9)*	72.4 (65.1-79.7)***	<0.001
Heavy smoker (≥15 vs. 0.1-14.9 pack-years smoked) (%)††	27.1 (24.1-30.1)	30.2 (25.1-35.2)	35.1 (26.0-44.3)	51.5 (40.6-62.3)***	<0.001
ETS (%)	57.1 (52.1-62.0)	60.0 (54.3-65.7)	58.3 (49.9-66.7)	66.0 (57.2-74.4)*	0.084
Occupational exposure (%)	42.0 (37.2-46.7)	45.9 (40.2-51.6)*	43.7 (35.2-52.2)	57.4 (48.1-66.7)***	0.001
Family asthma (%)	11.1 (9.9-12.3)	24.9 (21.6-28.1)***	26.3 (20.0-32.6)***	18.4 (12.1-24.7)**	<0.001
Respiratory infection in childhood (%)	8.7 (7.4-10.1)	17.4 (14.2-20.6)***	20.0 (14.0-25.9)***	13.0 (7.7-18.4)	<0.001
Mother smoking during subject's childhood (%)	18.6 (13.3-23.8)	19.1 (13.3-24.9)	20.3 (12.8-27.7)	17.5 (10.1-25.0)	0.89
Cat in childhood (%)	47.9 (44.3-51.4)	47.8 (43.2-52.4)	45.0 (37.4-52.6)	55.6 (47.2-64.1)	0.22

Dog in childhood (%)	49.1 (44.3-53.8)	48.4 (42.8-54.0)	43.8 (35.5-52.1)	50.7 (41.4-59.9)	0.54
Currently keeping a cat (%)	17.6 (14.5-20.6)	20.9 (16.8-25.1)*	15.6 (10.3-21.0)	12.0 (6.7-17.3)	0.013
Currently keeping a dog (%)	15.6 (13.1-18.2)	18.1 (14.6-21.7)	17.1 (11.7-22.5)	10.9 (5.7-16.1)	0.092
Mould in the house (%)	33.0 (28.4-37.6)	35.7 (30.1-41.3)	30.9 (23.1-38.6)	30.9 (22.1-39.7)	0.37

* $p<0.05$, ** $p<0.01$, *** $p<0.001$ for the comparison of the disease group with the "healthy" category

† adjusted by using a logistic regression model with the characteristic in the 1st column as the dependent variable, sex, age (with the exception of sex and age, only adjusted for age and sex, respectively), and disease status as independent variables, and a random intercept term for ECRHS centre and sample

‡ refers to the comparison across the groups. A $p<0.05$ indicates that at least one of the prevalence rates is significantly different from the others.

†† lifetime non-smokers excluded

Table 3. Sex- and age- adjusted prevalence rates with 95%CIs of clinical characteristics at baseline.†

	Healthy (n=5,659)	**Asthma alone** (n=941)	**ACOS** (n=218)	**COPD alone** (n=166)	**overall p-value‡**
Wheezing in the last 12months (%)	22.1 (18.1-26.0)	77.9 (73.3-82.5)***	87.3 (82.1-92.6)***	38.2 (28.7-47.7)***	<0.001
Trouble with breathing (%)	23.1 (18.5-27.7)	70.5 (64.5-76.5)***	79.2 (72.1-86.3)***	35.3 (25.3-45.3)**	<0.001
MRC dyspnoea score >1†† (%)	18.0 (15.0-21.1)	36.0 (30.5-41.4)***	38.3 (29.9-46.7)***	27.9 (19.5-36.3)**	<0.001
Chronic Bronchitis § (%)	11.1 (9.2-13.0)	25.0 (20.7-29.3)***	30.6 (23.3-38.0)***	22.9 (15.3-30.4)***	<0.001
AHR (%)	3.5 (2.8-4.2)	66.6 (62.0-71.4)***	92.1 (87.7-96.4)***	14.5 (7.5-21.4)***	<0.001
Allergic rhinitis (%)	24.1 (21.3-26.9)	60.5 (55.9-65.1)***	55.5 (47.8-63.3)***	24.7 (17.5-32.0)	<0.001
Lifetime eczema (%)	38.7 (35.3-42.1)	49.4 (44.8-54.0)***	45.0 (37.5-52.6)	39.1 (30.9-47.4)	<0.001
Allergen sensitization (%)	28.4 (25.7-31.1)	64.4 (60.2-68.6)***	67.4 (60.1-74.7)***	26.8 (19.1-34.4)	<0.001
Use of medicines (inhaler, oral, injection, suppository or other remedy) for breathing problems (%)	20.3 (15.3-25.3)	71.2 (64.4-78.1)***	75.8 (67.4-84.2)***	22.2 (13.0-31.4)	<0.001
Hospital/ER admission for breathing problems	5.0 (3.8-6.1)	22.6 (18.1-27.2)***	29.9 (22.2-37.6)***	6.9 (2.7-11.1)	<0.001

(%)					
FEV1 <80% predicted (%)	1.4 (1.0-1.8)	4.5 (3.1-6.0)***	33.1 (25.6-40.5)***	16.4 (10.3-22.5)***	<0.001
FVC <80% predicted (%)	1.0 (0.6-1.3)	1.3 (0.5-2.0)	3.4 (1.1-5.8)**	1.3 (0.0-2.9)	0.024
FEV1 % predicted	106.9 (105.9-107.9)	101.5 (100.3-102.7) ***	85.1 (83.2-86.9) ***	92.5 (90.5-94.6) ***	<0.001
FVC % predicted	109.0 (108.0-110.0)	106.9 (105.7-108.1) ***	107.6 (105.7-109.5)	112.3 (110.2-114.4) **	<0.001

* p<0.05, ** p<0.01, *** p<0.001 for the comparison of the disease group with the "healthy" category

† adjusted by using a logistic regression model with the characteristic in the 1st column as the dependent variable, sex, age and disease status as independent variables, and a random intercept term for ECRHS centre and sample

‡ refers to the comparison across the groups. A p<0.05 indicates that at least one of the prevalence rates is significantly different from the others

†† being troubled by shortness of breath when hurrying on level ground or walking up a slight hill

§ having cough or phlegm on most days for as long as three months each year for ≥2 years

Table 4. Mean change of lung function† and prevalence of hospital/ER admissions for breathing problems‡ over the follow-up, with 95%CIs.

	Healthy (n=5,659)	**Asthma alone** (n=941)	**ACOS** (n=218)	**COPD alone** (n=166)	**overall p-value††**
Mean FEV1 change (mL/year)	-26.2 (-31.1; -21.3)	-25.3 (-30.5; -20.1)	-25.9 (-32.2; -19.6)	-37.3 (-44.0; -30.6)***	<0.001
Mean FEV1 change (% of baseline/year)	-0.69 (-0.83; -0.55)	-0.68 (-0.83; -0.53)	-0.66 (-0.84; -0.47)	-1.17 (-1.37; -0.97)***	<0.001
Mean FVC change (mL/year)	-19.8 (-25.6; -14.1)	-21.3 (-27.4; -15.2)	-25.5 (-33.0; -18.0)*	-37.0 (-45.0; -29.0)***	<0.001
Mean FVC change (% of baseline/year)	-0.42 (-0.55; -0.29)	-0.45 (-0.59; -0.31)	-0.55 (-0.72; -0.38)*	-0.81 (-0.99; -0.63)***	<0.001
Hospital/ER admission for breathing problems§ (%)	3.6 (2.7; 4.5)	11.9 (8.7; 15.0)***	15.8 (9.9; 21.8)***	8.1 (3.5; 12.7)**	<0.001

* p<0.05, ** p<0.01, *** p<0.001 for the comparison of the disease group with the "healthy" category

† adjusted by using a linear regression model, with FEV1 or FVC change as dependent variable, sex, age, height and disease status as independent variables, and a random intercept term for ECRHS centre and sample. A negative value represents lung function decline

‡ adjusted by using a logistic regression model, with hospital/ER admissions as dependent variable, sex, age and disease status as independent variables, and a random intercept term for ECRHS centre and sample

†† refers to the comparison across the groups

§ present if a subject answered positively to one or both the questions "Since the last survey, have you spent a night in hospital / have you visited a hospital casualty department or ER because of breathing problems?"

Table 5. Mean change of lung function† and risk of hospital/ER admission for breathing problems‡ over the follow-up, with 95%CIs, for subjects with current asthma, COPD or both, compared with healthy subjects.

		Asthma alone	**ACOS**	**COPD alone**	**p-value heterogeneity††**
FEV1 change (mL/year)	mean difference (95%CI) with respect to the healthy category	0.69 (-1.65; 3.02)	1.62 (-2.76; 5.99)	-7.64 (-12.6; -2.66)**	0.007
FEV1 change (% of baseline/year)		0.004 (-0.07; 0.07)	0.05 (-0.08; 0.18)	-0.37 (-0.52; -0.22)***	<0.001
FVC change (mL/year)		-0.92 (-3.79; 1.96)	-4.84 (-10.23; 0.54)	-13.83 (-19.96; -7.70)***	<0.001
FVC change (% of baseline/year)		-0.01 (-0.08; 0.05)	-0.11 (-0.23; 0.01)	-0.30 (-0.43; -0.16)***	<0.001
Hospital/ER admission for breathing problems§	OR (95%CI) with respect to the healthy category	3.76 (2.84; 4.99)***	5.12 (3.24; 8.10)***	2.10 (1.06; 4.13)*	0.080

* p<0.05, ** p<0.01, *** p<0.001 for the comparison of the disease group with the "healthy" category

† regression coefficients obtained by using a linear regression model, with FEV1 or FVC change as dependent variable, sex, age, height, BMI, education level, occupational exposure to vapours, gas, dust or fumes, disease status at baseline; lifetime smoking exposure (5-level variable coded as: 0, lifetime non-smoker; past-smoker with 1, <15 p-y smoked or 2, ≥15 p-y smoked; current smoker with 3, <15 p-y smoked or 4, ≥15 p-y

smoked) and change in BMI over the follow-up as independent variables, and a random intercept term for ECRHS centre and sample. A negative value represents a greater decline with respect to the healthy reference category

‡ ORs obtained by using a logistic regression model, with hospital/ER admissions as dependent variable, sex, age, BMI, education level, occupational exposure to vapours, gas, dust or fumes, disease status at baseline; lifetime smoking exposure, and change in BMI over the follow-up as independent variables, and a random intercept term for ECRHS centre and sample

†† p-value for the heterogeneity of the association across the groups, obtained by testing the difference across regression coefficients using Wald test. A $p<0.05$ indicates that at least one of the regression coefficients is significantly different from the others, i.e. that the change in lung function (or risk of hospital/ER admissions) with respect to the reference healthy category differs for at least one disease group as compared to the others

§ present if a subject answered positively to one or both the questions “Since the last survey, have you spent a night in hospital / have you visited a hospital casualty department or ER because of breathing problems?”

ONLINE SUPPLEMENTARY MATERIAL

Title Asthma, COPD, and overlap syndrome: a longitudinal study in young European adults

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1) Validity of the definition of chronic airflow obstruction

The European Community Respiratory Health Survey (ECRHS) III is a follow-up prospective survey (2010-2014) of all subjects who underwent examination in ECRHS I (www.ecrhs.org). The maximum FEV1 and FVC before and 15 min after the administration of a bronchodilator (Salbutamol, 400 μg) were measured. All study participants gave their written informed consent.
We evaluated the validity of the definition of *chronic airflow obstruction* using preliminary lung function data from the ECRHS III. We defined *chronic airflow obstruction* at ECRHS III (present if pre-bronchodilator FEV1/FVC <lower limit of normal [LLN] both at ECRHS II and at ECRHS III; absent if pre-bronchodilator FEV1/FVC ≥LLN at ECRHS III). The "gold standard" for comparison was *fixed airflow obstruction* at ECRHS III defined according to post-bronchodilator spirometry (FEV1/FVC< LLN). The LLN was defined according to the reference values by Kuster et al. (2008), which have been derived for an age range (18-80 years) that includes the ages of all subjects participating in ECRHS between 1991 and 2014.
We included in the analysis all the 3,287 subjects who participated both in ECRHS II and ECRHS III and had pre- and post-bronchodilator lung function measurements available (2,911 without asthma + 376 with asthma) (Table S1). We repeated this analysis using the GOLD fixed cut-off definition of airflow obstruction (FEV1/FVC <0.70) (Table S2).

Table S1: Validity* of the definition of pre-bronchodilator chronic airflow obstruction as compared to post-bronchodilator airflow obstruction at ECRHS III: *LLN criterion*.

	N	N. subjects with fixed airflow obstruction	Sensitivity	Specificity	Positive predictive value	Negative predictive value
All subjects	3,287	162	80.2	98.3	71.0	99.0
Subjects without asthma	2,911	103	76.7	98.8	69.3	99.1
Subjects with asthma	376	59	86.4	94.3	73.9	97.4

* analysis based on ECRHS III preliminary lung function data.

Table S2: Validity* of the definition of pre-bronchodilator chronic airflow obstruction as compared to post-bronchodilator airflow obstruction at ECRHS III: *GOLD criterion*.

	N	N. subjects with fixed airflow obstruction	Sensitivity	Specificity	Positive predictive value	Negative predictive value
All subjects	3,147	188	77.7	98.5	76.8	98.6
Subjects without asthma	2,786	123	73.2	98.8	74.4	98.8
Subjects with asthma	361	65	86.2	95.6	81.2	96.9

* analysis based on ECRHS III preliminary lung function data.

2) Stability of disease definitions over time

To evaluate whether disease status was stable over the study period, we re-assessed subjects' disease status at follow-up. Subjects were classified at follow-up (ECRHS II) using similar definitions of current asthma, COPD, and the ACOS that we used at baseline (ECRHS I) (see Methods of the manuscript), and then their disease status at baseline and follow-up were compared. For disease classification at follow-up, we used data on asthma, respiratory symptoms, AHR and use of medicines derived from ECRHS II (to account for *current* disease manifestations). Information on history of active smoking or occupational exposures were derived combining data from ECRHS I and II (to account for *cumulative* exposures). The definition of chronic airflow obstruction was the same (pre-bronchodilator FEV1/FVC< LLN both at baseline and at follow-up).

The results of this analysis are shown in Table S3. Information to classify disease status at both surveys was available for 6,859 (98%) subjects. Most of the subjects that were in one disease group at baseline were still classified in the same disease group at follow-up: percentages of subjects with unchanged classification ranged between 75.7% (COPD alone) and 93.0% (healthy subjects). Most subjects with ACOS were still classified in this group at follow-up (83.9%), while some were re-classified as having current asthma alone (3.3%) or COPD alone (12.8%).

Table S3: comparison of the disease status at baseline and follow-up.

		Disease status at follow-up				
		Healthy	**Asthma alone**	**ACOS**	**COPD alone**	**Total**
Disease status at baseline	**Healthy**	**5,218 (93.0%)**	392 (7.0%)	0 (0.0%)	0 (0.0%)	5,610 (100%)
	Asthma alone	197 (22.2%)	**683 (77.1%)**	5 (0.6%)	1 (0.1%)	886 (100%)
	ACOS	0 (0.0%)	7 (3.3%)	**177 (83.9%)**	27 (12.8%)	211 (100%)
	COPD alone	0 (0%)	0 (0%)	37 (24.3%)	**115 (75.7%)**	152 (100%)

3) Questionnaire information

Based on the answers to the questions of the clinical interview, the following variables were derived for each subject:

- age and sex;
- lifetime asthma (positive answer to the question “Have you ever had asthma?”);
- asthma-like symptoms in the last 12 months (wheezing or whistling in the chest; chest tightness; shortness of breath at rest; shortness of breath following strenuous activity, woken up by shortness of breath);
- use of inhaled/oral medicines to help breathing in the last 12 months;
- chronic bronchitis (having cough or phlegm on most days for as long as three months each year for ≥2 years);
- a Medical Research Council (MRC) dyspnea score >1 (being troubled by shortness of breath when hurrying on level ground or walking up a slight hill);
- allergic rhinitis (the presence of nasal allergies, including hay fever);
- lifetime eczema (having ever had eczema or any kind of skin allergy);
- a low education level (having completed full-time education before the age of 16);
- occupational exposure to vapors, gas, dust or fumes (positive answer to “Have you ever worked in a job which exposed you to vapors, gas, dust or fumes?);
- lifetime smoking exposure: 0) lifetime non-smoker; past-smoker with 1) <15 p-y smoked or 2) ≥15 p-y smoked; current smoker with 3) <15 p-y smoked or 4) ≥15 p-y smoked;
- environmental tobacco smoke (ETS) exposure (having been regularly exposed to tobacco smoke in the last 12 months);
- family asthma (having reported asthma in father and/or mother);
- respiratory infection in childhood (having had a serious respiratory infection before the age of five years);
- having a mother who smoked regularly during childhood or before the subject was born;
- exposure to cat/dog in childhood (anyone in the household kept a cat/dog during subject’s childhood);
- currently keeping a cat/dog;
- mold in the house (positive answer to “Has there ever been any mold or mildew on any surface, other than food, inside the home?”);
- hospitalization or Emergency Room (ER) visits for respiratory problems during the follow-up (positive answer to one or both of the questions “Since the last survey, have you spent a night in hospital / have you visited a hospital casualty department or ER because of breathing problems?”).

Table S4: Baseline (ECRHS I) characteristics of the subjects according to their participation in ECRHS II.

	Non-participating in ECRHS II (n=7,423)	**Participating in ECRHS II** (n=10,933)	**p-value**
Female gender (n, %)	3,878 (52)	5,808 (53)	0.24
Age (yr)*	33.2 ± 7.2	34.1 ± 7.1	<0.001
Body mass index (kg/m^2)*	23.9 ±4.1	24.1 ± 4.0	0.006
Low education (n, %)	767 (13)	1,374 (13)	0.91
Smoking habits (n, %)			
non-smoker	2,876 (40)	4,860 (45)	<0.001
< 15 pack-yrs	2,769 (38)	3,846 (36)	
≥ 15 pack-yrs	1,614 (22)	2,043 (19)	
Sensitization to allergens (n, %)	1,763 (35)	3,100 (34)	0.30
FEV1 % predicted*	103.9 ± 14.4	105.0 ± 14.0	<0.001
Airway hyper-responsiveness (n, %)	758 (17)	1,284 (16)	0.28

* mean ± SD reported

Table S5. Distribution (n, %) of the subjects by the sub-definition(s) of current asthma and COPD they fulfilled.[a]

Disease	**Sub-definitions**	**Asthma alone** (n=941)	**ACOS** (n=218)	**COPD alone** (n=166)
Current asthma	"ever asthma" + asthma-like symptoms/asthma attacks	666 (70.8%)	169 (77.5%)	-
	"ever asthma" + medicines for breathing problems	541 (57.5%)	148 (67.9%)	-
	"ever asthma" + AHR	317 (33.7%)	87 (39.9%)	-
	"ever asthma" + transient airflow obstruction	84 (8.9%)	-	-
	asthma-like symptoms + AHR	511 (54.3%)	131 (60.1%)	-
COPD	chronic airflow obstruction + history of symptoms	-	199 (91.3%)	93 (56.0%)
	chronic airflow obstruction + history of exposures	-	149 (68.3%)	139 (83.7%)

[a] subjects can fulfil more than one sub-definition of current asthma or COPD (e.g. subjects with "ever asthma" + asthma-like symptoms + use of respiratory medicines will fulfil both the first and second sub-definitions of "current asthma")

Table S6. Sex- and age- adjusted prevalence rates with 95%CIs of socio-demographic characteristics, environmental exposures and risk factors at baseline: sensitivity analysis based on alternative disease definitions.†

	Healthy (n=5,883)	**Asthma alone** (n=775)	**ACOS** (n=181)	**COPD alone** (n=276)	**overall p-value‡**
Female gender (%)	52.8 (51.3-54.2)	59.1 (55.6-62.6)**	46.9 (39.6-54.2)	54.0 (48.1-60.0)	0.003
Age (>35 y) (%)	50.6 (47.6-53.5)	44.1 (39.8-48.5)**	45.8 (37.9-53.6)	56.1 (49.6-62.6)	0.002
Low education (%)	6.9 (3.8-10.0)	6.4 (3.1-9.7)	6.4 (2.3-10.5)	7.7 (3.3-12.2)	0.88
Lifetime smoker (>0 vs. 0 pack-years smoked) (%)	56.1 (53.6-58.6)	51.1 (46.9-55.3)*	58.5 (50.8-66.1)	65.0 (58.9-71.1)**	0.001
Heavy smoker (≥15 vs. 0.1-14.9 pack-years smoked) (%)††	28.2 (25.1-31.2)	25.2 (20.0-30.4)	27.0 (17.6-36.4)	45.4 (36.6-54.3)***	<0.001
ETS (%)	58.1 (53.3-63.0)	56.3 (50.3-62.3)	52.9 (43.7-62.1)	60.4 (52.8-68.0)	0.44
Occupational exposure (%)	42.2 (37.4-46.9)	46.2 (40.2-52.2)*	43.6 (34.4-52.8)	40.2 (32.5-47.8)	0.28
Family asthma (%)	11.4 (10.2-12.6)	26.2 (22.6-29.8)***	29.7 (22.6-36.9)***	17.5 (12.7-22.3)**	<0.001
Respiratory infection in childhood (%)	8.7 (7.4-10.0)	19.9 (16.2-23.5)***	20.7 (14.1-27.3)***	12.1 (8.0-16.2)	<0.001
Mother smoking during subject's childhood (%)	18.9 (13.6-24.2)	18.8 (13.0-24.6)	17.5 (10.4-24.7)	18.9 (12.0-25.7)	0.97
Cat in childhood (%)	48.1 (44.6-51.7)	46.1 (41.2-50.9)	45.2 (37.0-53.5)	50.0 (43.0-56.9)	0.63
Dog in childhood (%)	49.3 (44.5-54.1)	46.8 (40.9-52.6)	42.1 (33.3-51.0)	50.5 (42.8-58.3)	0.25
Currently keeping a cat (%)	18.0 (14.9-21.2)	19.5 (15.3-23.7)	14.2 (8.7-19.6)	16.0 (11.0-21.1)	0.26
Currently keeping a dog (%)	15.9 (13.4-18.5)	17.7 (14.0-21.4)	15.7 (10.1-21.3)	11.9 (7.6-16.2)	0.17
Mould in the house (%)	33.9 (29.1-38.6)	32.7 (27.1-38.4)	30.2 (22.0-38.4)	32.3 (24.8-39.9)	0.74

* p<0.05, ** p<0.01, *** p<0.001 for the comparison of the disease group with the "healthy" category

† Asthma alone = reported to have ever had asthma; COPD alone = chronic airflow obstruction; ACOS = asthma + COPD; Healthy = neither asthma nor COPD. Same statistical analysis done in Table 2 of the manuscript

‡ refers to the comparison across the groups.

†† lifetime non-smokers excluded

Table S7. Sex- and age- adjusted prevalence rates with 95%CIs of clinical characteristics at baseline: sensitivity analysis based on alternative disease definitions.†

	Healthy (n=5,883)	**Asthma alone** (n=775)	**ACOS** (n=181)	**COPD alone** (n=276)	**overall p-value‡**
Wheezing in the last 12months (%)	25.5 (21.0-30.0)	72.7 (67.1-78.3)***	86.9 (80.9-93.0)***	42.5 (34.1-51.0)***	<0.001
Trouble with breathing (%)	25.1 (20.1-30.1)	71.8 (65.7-78.0)***	83.2 (76.2-90.2)***	31.0 (22.7-39.3)	<0.001
MRC dyspnoea score >1†† (%)	18.7 (15.5-21.9)	35.7 (29.8-41.5)***	39.3 (30.2-48.5)***	25.4 (18.6-32.1)*	<0.001
Chronic Bronchitis § (%)	11.9 (9.8-13.9)	23.9 (19.4-28.4)***	29.0 (21.2-36.8)***	19.3 (13.5-25.2)**	<0.001
AHR (%)	8.7 (7.1-10.2)	48.1 (42.3-53.9)***	84.0 (76.3-91.7)***	38.5 (30.4-46.6)***	<0.001
Allergic rhinitis (%)	25.0 (22.1-27.8)	64.3 (59.6-69.0)***	63.1 (55.0-71.3)***	24.6 (18.8-30.4)	<0.001
Lifetime eczema (%)	38.8 (35.5-42.2)	50.8 (46.0-55.7)***	47.9 (39.6-56.2)*	37.1 (30.5-43.7)	<0.001
Allergen sensitization (%)	29.4 (26.7-32.1)	66.9 (62.5-71.3)***	75.6 (68.4-82.9)***	30.5 (24.2-36.9)	<0.001
Use of medicines (inhaler, oral, injection, suppository or other remedy) for breathing problems (%)	21.8 (16.4-27.1)	74.4 (67.7-81.1)***	84.5 (77.3-91.6)***	26.1 (17.5-34.7)	<0.001
Hospital/ER admission for breathing problems (%)	5.0 (3.9-6.1)	27.8 (22.5-33.1)***	35.5 (26.7-44.3)***	6.3 (3.1-9.5)	<0.001
FEV1 <80% predicted (%)	1.4 (1.1-1.8)	4.4 (2.9-6.0)***	37.9 (29.6-46.1)***	14.9 (10.2-19.6)***	<0.001
FVC <80% predicted (%)	1.0 (0.6-1.3)	1.3 (0.5-2.0)	4.1 (1.3-7.0)***	0.9 (0.0-1.8)	0.008
FEV1 % predicted	106.5 (105.4-107.5)	102.4 (101.1-103.7)***	84.3 (82.2-86.3)***	92.7 (91.0-94.5)***	<0.001

FVC % predicted	108.8 (107.8-109.8)	107.3 (106.0-108.6)**	107.5 (105.5-109.6)	112.3 (110.5-114.0)***	<0.001

* p<0.05, ** p<0.01, *** p<0.001 for the comparison of the disease group with the “healthy” category

† Asthma alone = reported to have ever had asthma; COPD alone = chronic airflow obstruction; ACOS = asthma + COPD; Healthy = neither asthma nor COPD. Same statistical analysis done in Table 3 of the manuscript

‡ refers to the comparison across the groups.

†† being troubled by shortness of breath when hurrying on level ground or walking up a slight hill

§ having cough or phlegm on most days for as long as three months each year for ≥2 years

Table S8: Mean change of lung function and risk of hospital/ER admission for breathing problems over the follow-up, with 95%CIs, for subjects with asthma, COPD or both, compared with healthy subjects: sensitivity analysis based on alternative disease definitions.†

		Asthma alone	**ACOS**	**COPD alone**	**p-value heterogeneity††**
FEV1 change (mL/year)	mean difference (95%CI) with respect to the healthy category	-0.93 (-3.47; 1.60)	3.30 (-1.48; 8.07)	-4.89 (-8.72; -1.07)*	0.027
FEV1 change (% of baseline/year)		-0.04 (-0.11; 0.04)	0.12 (-0.03; 0.26)	-0.25 (-0.37; -0.14)***	<0.001
FVC change (mL/year)		-2.49 (-5.60; 0.61)	-3.62 (-9.50; 2.26)	-10.90 (-15.61; -6.19)***	0.010
FVC change (% of baseline/year)		-0.05 (-0.11; 0.02)	-0.09 (-0.22; 0.04)	-0.23 (-0.34; -0.13)***	0.010
Hospital/ER admission for breathing problems§	OR (95%CI) with respect to the healthy category	3.81 (2.83; 5.13)***	5.68 (3.52; 9.16)***	1.97 (1.14; 3.38)*	0.010

* p<0.05, ** p<0.01, *** p<0.001 for the comparison of the disease group with the "healthy" category

† Asthma alone = reported to have ever had asthma; COPD alone = chronic airflow obstruction; ACOS = asthma + COPD; Healthy = neither asthma nor COPD. Same statistical analysis done in Table 5 of the manuscript

†† p-value for the heterogeneity of the association across the groups, obtained by testing the difference across regression coefficients by using Wald test. A p<0.05 indicates that at least one of the regression coefficients is significantly different from the others

Reference

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