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

Roberto de Marco¹, Alessandro Marcon¹, Andrea Rossi², Josep M. Antó³,4,5,6, Isà Cerverì⁷, Thorarinn Gislason⁸, Joachim Heinrich⁹,10, Christfer Janson¹¹, Deborah Jarvis¹², Nino Kuenzli¹³,14, Bénédicte Leynaert¹⁵, Nicole Probst-Hensch¹³,14, Cecilie Svanes¹⁶,17, Matthias Wjst¹⁸,19 and Peter Burney¹²

Affiliations: ¹Unit of Epidemiology and Medical Statistics, Department of Public Health and Community Medicine, University of Verona, Verona, Italy. ²Pulmonary Unit, Azienda Ospedaliera Universitaria Integrata and University of Verona, Verona, Italy. ³Centre for Research in Environmental Epidemiology (CREDAS), Barcelona, Spain. ⁴Hospital del Mar Medical Research Institute, Barcelona, Spain. ⁵Universitat Pompeu Fabra, Barcelona, Spain. ⁶CIBER Epidemiologia y Salud Pública (CIBERESP), Barcelona, Spain. ⁷Istituto di Ricovero e Cura a Carattere Scientifico San Matteo Hospital Foundation, University of Pavia, Pavia, Italy. ⁸Department of Respiratory Medicine and Sleep, Landspitali University Hospital and Faculty of Medicine, University of Iceland, Reykjavik, Iceland. ⁹Institute of Epidemiology I, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Munich, Germany. ¹⁰Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Inner City Clinic, University Hospital of Munich, Ludwig-Maximilians University (LMU), Munich, Germany. ¹¹Department of Medical Sciences: Respiratory Medicine and Allergology, Uppsala University Hospital, Uppsala, Sweden. ¹²Respiratory Epidemiology and Public Health Group, National Heart and Lung Institute, Imperial College, London, UK. ¹³Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Basel, Switzerland. ¹⁴University of Basel, Basel, Switzerland. ¹⁵Inserm-U1152-Epidemiology, Institut National de la Santé et de la Recherche Médicale, Faculté Paris Diderot, Paris, France. ¹⁶Bergen Respiratory Research Group, Centre for International Health, University of Bergen, Bergen, Norway. ¹⁷Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway. ¹⁸Comprehensive Pneumology Center, Institute of Lung Biology and Disease, Helmholtz Zentrum Muenchen, German Research Center for Environmental Health, Munich, Germany. ¹⁹Institute of Medical Statistics and Epidemiology, Technische Universitaet Muenchen, Munich, Germany.

Correspondence: Roberto de Marco, Unit of Epidemiology and Medical Statistics, Department of Public Health and Community Medicine, University of Verona, c/o Istituti Biologici II, Strada Le Grazie 8, 37134 Verona, Italy. E-mail: roberto.demarco@univr.it

ABSTRACT We compared risk factors and clinical characteristics, 9-year lung function change and hospitalisation risk across subjects with the asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS), asthma or COPD alone, or none of these diseases.

Participants in the European Community Respiratory Health Survey in 1991–1993 (aged 20–44 years) and 1999–2001 were included. Chronic airflow obstruction was defined as pre-bronchodilator forced expiratory volume in 1 s (FEV1)/forced vital capacity<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=5659).

Subjects with ACOS shared risk factors and clinical characteristics with subjects with asthma alone, but they had an earlier age of asthma onset. FEV1 change in the ACOS group (~−25.9 mL·year⁻¹) was similar to that in the asthma group (~−25.3 mL·year⁻¹), and lower (p<0.001) than in the COPD group (~−37.3 mL·year⁻¹). ACOS was associated with the highest hospitalisation rate.

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

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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, comorbidities and healthcare utilisation, 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 (aged 20–44 years) 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; “baseline” examination). 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 forced expiratory volume in 1 s (FEV1) and forced vital capacity (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]. AHR was defined as a decrease of 20% in FEV1 after a cumulative methacholine dose ⩽1 mg. Allergen sensitisation was present if levels of serum immunoglobulin E for house dust mite, cat dander, Timothy grass or Cladosporium species were >0.35 kU·L⁻¹. 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 of asthma-like symptoms (wheezing/whistling in the chest, chest tightness, shortness of breath at rest/following strenuous activity/at night-time or asthma attacks); use of inhaled/oral medicines for breathing problems in the last year; AHR; or transient airflow obstruction; or 2) she/he reported asthma-like symptoms in the last year AND 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 either 1) symptoms (shortness of breath after strenuous activity, dyspnoea (trouble with breathing) or chronic bronchitis (having cough or phlegm on most days for as long as 3 months each year for ⩾2 years)); or 2) 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 vapours, gas, dust or fumes?").

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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 (online supplementary material) suggest that “chronic airflow obstruction” is a valid measurement of fixed airflow obstruction (sensitivity 80.2% and 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); and 4) COPD alone (COPD without asthma).

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

The longitudinal outcomes were as follows. 1) Absolute FEV1 (and FVC) change over follow-up ((value_{follow-up} − value_{baseline})/follow-up time) (mL·year^{-1}) and FEV1 (and FVC) change as a percentage of baseline value (100×(value_{follow-up} − value_{baseline})/(value_{baseline} × follow-up time)) (percentage per year). Negative values represent decline. 2) Risk (%) of hospitalisations and/or 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 and 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 hospitalisation rates, respectively, as dependent variables, and disease status as the main independent variable. Adjustment variables were age, height and 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 versus symptomatic) [22]. Missing values were deleted listwise. The statistical analyses were performed using Stata 13.1 (StataCorp, College Station, TX, USA).

In sensitivity analyses, 1) 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); and 2) ECRHS centres were set as a random intercept and type of sample was set as a fixed effect.

**Results**

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 (fig. 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 (online supplementary table S4). Mean±SD follow-up time was 9±1 years (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 (fig. 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). Disease status was relatively stable over time (online supplementary 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 (mean±SD 33.6±7.2 years) 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 (interquartile range) 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 at asthma onset (14.9 versus 17.2 years, \( p=0.016 \)), a longer disease duration (27.7 versus 24.8 years, \( p=0.003 \)), a greater percentage of inhaled corticosteroid use (30.2 versus 20.6%, \( p=0.003 \)) and more frequent asthma attacks in the last year (11.2 versus 6.2, \( p=0.034 \)).

The prevalence rates of wheezing, dyspnoea, chronic bronchitis, allergic rhinitis, eczema and allergen sensitisation, 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 (\( p<0.001 \)).

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### TABLE 1
Baseline [European Community Respiratory Health Survey (ECRHS) I] characteristics of the subjects participating in ECRHS II

<table>
<thead>
<tr>
<th></th>
<th>Subjects included in the analyses</th>
<th>Subjects not included in the analyses</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>6984</td>
<td>3949</td>
<td>0.93</td>
</tr>
<tr>
<td>Female</td>
<td>3708 (53)</td>
<td>2100 (53)</td>
<td></td>
</tr>
<tr>
<td>Age years</td>
<td>34.3±7.1</td>
<td>33.7±7.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI kg·m(^{-2})</td>
<td>24.1±4.0</td>
<td>24.1±4.0</td>
<td>0.53</td>
</tr>
<tr>
<td>Low education</td>
<td>875 (13)</td>
<td>499 (13)</td>
<td>0.83</td>
</tr>
<tr>
<td>Smoking habits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>3067 (45)</td>
<td>1793 (46)</td>
<td>0.16</td>
</tr>
<tr>
<td>&lt;15 pack-years</td>
<td>2499 (36)</td>
<td>1347 (35)</td>
<td></td>
</tr>
<tr>
<td>≥15 pack-years</td>
<td>1321 (19)</td>
<td>722 (19)</td>
<td></td>
</tr>
<tr>
<td>Sensitisation to allergens</td>
<td>2130 (34)</td>
<td>970 (35)</td>
<td>0.49</td>
</tr>
<tr>
<td>FEV1 % predicted</td>
<td>105.0±13.5</td>
<td>105.0±15.2</td>
<td>0.95</td>
</tr>
<tr>
<td>AHR</td>
<td>886 (15)</td>
<td>398 (18)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are presented as n, n (%) or mean±SD, unless otherwise stated. BMI: body mass index; FEV1: forced expiratory volume in 1 s; AHR: airway hyperresponsiveness.
TABLE 2 Sex- and age-adjusted prevalence of sociodemographic characteristics, environmental exposures and risk factors at baseline

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>Asthma alone</th>
<th>ACOS</th>
<th>COPD alone</th>
<th>Overall p-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>5659</td>
<td>941</td>
<td>218</td>
<td>164</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>52.2</td>
<td>50.8–53.6</td>
<td>61.2 (58.0–64.3)**</td>
<td>47.7 (41.0–54.3)</td>
<td>47.5 (39.9–55.2) &lt;0.001</td>
</tr>
<tr>
<td>Age &gt;35 years</td>
<td>50.8</td>
<td>47.8–53.7</td>
<td>44.2 (40.1–48.2)**</td>
<td>50.5 (43.2–57.7)</td>
<td>60.4 (52.5–68.3)* &lt;0.001</td>
</tr>
<tr>
<td>Low education</td>
<td>6.7</td>
<td>3.7–9.8</td>
<td>7.4 (3.8–11.0)</td>
<td>7.9 (3.3–12.5)</td>
<td>7.0 (2.4–11.7)   0.80</td>
</tr>
<tr>
<td>Lifetime smoker (≥0 pack-years smoked)</td>
<td>55.1</td>
<td>52.6–57.7</td>
<td>56.5 (52.6–60.3)</td>
<td>64.1 (57.3–70.9)*</td>
<td>72.4 (65.1–79.7)** &lt;0.001</td>
</tr>
<tr>
<td>Heavy smoker (≥15 versus 0.1–14.9 pack-years smoked)#</td>
<td>27.1</td>
<td>24.1–30.1</td>
<td>30.2 (25.1–35.2)</td>
<td>35.1 (26.0–44.3)</td>
<td>51.5 (40.6–62.3)** &lt;0.001</td>
</tr>
<tr>
<td>ETS</td>
<td>57.1</td>
<td>52.1–62.0</td>
<td>60.0 (54.3–65.7)</td>
<td>58.3 (49.9–66.7)</td>
<td>66.0 (57.2–74.4)* 0.084</td>
</tr>
<tr>
<td>Occupational exposure to vapours, dust, gas or fumes</td>
<td>42.0</td>
<td>37.2–46.7</td>
<td>45.9 (40.2–51.6)**</td>
<td>43.7 (35.2–52.2)</td>
<td>57.4 (48.1–66.7)** 0.001</td>
</tr>
<tr>
<td>Family asthma</td>
<td>11.1</td>
<td>9.9–12.3</td>
<td>24.9 (21.6–28.1)**</td>
<td>26.3 (20.0–32.6)**</td>
<td>18.4 (12.1–24.7)** &lt;0.001</td>
</tr>
<tr>
<td>Respiratory infection in childhood</td>
<td>8.7</td>
<td>7.4–10.1</td>
<td>17.4 (14.2–20.6)**</td>
<td>20.0 (14.0–25.9)**</td>
<td>13.0 (7.7–18.4) &lt;0.001</td>
</tr>
<tr>
<td>Mother smoked during subject’s childhood</td>
<td>18.6</td>
<td>13.3–23.8</td>
<td>19.1 (13.3–24.9)</td>
<td>20.3 (12.8–27.7)</td>
<td>17.5 (10.1–25.0) 0.89</td>
</tr>
<tr>
<td>Cat in childhood</td>
<td>47.9</td>
<td>44.3–51.4</td>
<td>47.9 (43.2–52.4)</td>
<td>45.0 (37.4–52.6)</td>
<td>55.6 (47.2–64.1) 0.22</td>
</tr>
<tr>
<td>Dog in childhood</td>
<td>49.1</td>
<td>44.3–53.8</td>
<td>48.6 (42.8–54.0)</td>
<td>43.8 (35.5–52.1)</td>
<td>50.7 (41.4–59.9) 0.54</td>
</tr>
<tr>
<td>Currently keeping a cat</td>
<td>17.6</td>
<td>14.5–20.6</td>
<td>20.9 (16.8–25.1)*</td>
<td>15.6 (10.3–21.0)</td>
<td>12.0 (6.7–17.3) 0.013</td>
</tr>
<tr>
<td>Currently keeping a dog</td>
<td>15.6</td>
<td>13.1–18.2</td>
<td>18.1 (14.6–21.7)</td>
<td>17.1 (11.7–22.5)</td>
<td>10.9 (5.7–16.1) 0.092</td>
</tr>
<tr>
<td>Mould in the house</td>
<td>33.0</td>
<td>28.4–37.6</td>
<td>35.7 (30.1–41.3)</td>
<td>30.9 (23.1–38.6)</td>
<td>30.9 (22.1–39.7) 0.37</td>
</tr>
</tbody>
</table>

Data are presented as n or % [95% CI], unless otherwise stated. Data were adjusted using logistic regression models with the characteristic in the first column as the dependent variable, sex, age [with the exception of sex and age, which were only adjusted for age and sex, respectively], and disease status as independent variables, and a random intercept term for European Community Respiratory Health Survey centre and sample. ACOS: asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome; ETS: environmental tobacco smoke. *: refers to the comparison across the groups; p<0.05 indicates that at least one of the prevalence rates is significantly different from the others; #: lifetime nonsmokers excluded. *: p<0.05; **: p<0.01; ***: p<0.001 for the comparison of the disease group with the healthy category.

Change in lung function and risk of hospitalisation

Mean change in FEV1 and hospitalisation rates at 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⁻¹ 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⁻¹ greater (p<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 two-fold, four-fold, and five-fold greater risk of reporting hospital/ER admissions over the follow-up, respectively, with respect to the reference group (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 (online supplementary tables S6 and S7), 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 hospitalisation 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 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.
As far as we know, studies on ACOS were usually cross-sectional and based on selected groups of elderly alone [7, 24], raised the hypothesis that ACOS could be a specific disease entity [12, 13, 25].

**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

### TABLE 3  Sex- and age-adjusted prevalence of clinical characteristics at baseline

| Subjects                                      | Healthy | Asthma alone | ACOS | COPD alone | Overall p-value*
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheezing in the last 12 months</td>
<td>5659</td>
<td>941</td>
<td>218</td>
<td>166</td>
<td></td>
</tr>
<tr>
<td>Trouble with breathing</td>
<td>22.1 (18.1–26.0)</td>
<td>77.9 (73.3–82.5)**</td>
<td>87.3 (82.1–92.6)**</td>
<td>38.2 (28.7–47.7)**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MRC dyspnoea score &gt;1§</td>
<td>23.1 (18.5–27.7)</td>
<td>70.5 (64.5–76.5)**</td>
<td>79.2 (72.1–86.3)**</td>
<td>35.3 (25.3–45.3)**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic bronchitis*</td>
<td>18.0 (10.5–21.1)</td>
<td>36.0 (30.5–41.4)**</td>
<td>38.3 (29.9–46.7)**</td>
<td>27.9 (19.5–36.3)**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AHR</td>
<td>11.1 (9.2–13.0)</td>
<td>25.0 (20.7–29.3)**</td>
<td>30.6 (23.3–38.0)**</td>
<td>22.9 (15.3–30.4)**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>3.5 (2.8–4.2)</td>
<td>66.6 (62.0–71.4)**</td>
<td>92.1 (87.7–96.4)**</td>
<td>14.5 (7.5–21.4)**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Allergic sensitisation</td>
<td>24.1 (21.3–26.9)</td>
<td>60.5 (55.9–65.1)**</td>
<td>55.5 (47.8–63.3)**</td>
<td>24.7 (17.5–32.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lifetime eczema</td>
<td>38.7 (35.3–42.1)</td>
<td>49.4 (44.8–54.0)**</td>
<td>45.0 (37.5–52.6)</td>
<td>39.1 (30.9–47.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of medicines (inhaled, oral, injection, suppository or other remedy) for breathing problems</td>
<td>28.4 (25.7–31.1)</td>
<td>64.4 (60.2–68.6)**</td>
<td>67.4 (60.1–74.7)**</td>
<td>26.8 (19.1–34.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hospital/ER admission for breathing problems</strong></td>
<td>20.3 (15.3–25.3)</td>
<td>71.2 (64.4–78.1)**</td>
<td>75.8 (67.4–84.2)**</td>
<td>22.2 (13.0–31.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as n or % (95% CI), unless otherwise stated. Data were adjusted by using logistic regression models with the characteristic in the first column as the dependent variable, sex, age and disease status as independent variables, and a random intercept term for European Community Respiratory Health Survey centre and sample. ACOS: asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome; MRC: Medical Research Council; AHR: airway hyperresponsiveness; ER: emergency room; FEV1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity. *: refers to the comparison across the groups; 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 3 months each year for 2 years. *: p<0.05; **: p<0.01; ***: p<0.001 for the comparison of the disease group with the healthy category.

### TABLE 4  Change of lung function and prevalence of hospital/emergency room (ER) admissions for breathing problems over follow-up

| Subjects                                      | Healthy | Asthma alone | ACOS | COPD alone | Overall p-value*
<table>
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<tbody>
<tr>
<td>FEV1 change mL·year⁻¹</td>
<td>−26.2 [−31.1–−21.3]</td>
<td>−25.3 [−30.5–−20.1]</td>
<td>−25.9 [−32.2–−19.6]</td>
<td>−37.3 [−44.0–−30.6]***</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1 change % of baseline-year⁻³</td>
<td>−0.69 [−0.83–−0.55]</td>
<td>−0.68 [−0.83–−0.53]</td>
<td>−0.66 [−0.84–−0.47]</td>
<td>−1.17 [−1.37–−0.97]***</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FVC change mL·year⁻¹</td>
<td>−19.8 [−25.6–−14.1]</td>
<td>−21.3 [−27.4–−15.2]</td>
<td>−25.5 [−33.0–−18.0]</td>
<td>−37.0 [−45.0–−29.0]***</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FVC change % of baseline-year⁻¹</td>
<td>−0.42 [−0.55–−0.29]</td>
<td>−0.45 [−0.59–−0.31]</td>
<td>−0.55 [−0.72–−0.38]</td>
<td>−0.81 [−0.99–−0.63]***</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital/ER admission for breathing problems%</td>
<td>3.6 [2.7–4.5]</td>
<td>11.9 [8.7–15.0]**</td>
<td>15.8 [9.9–21.8]**</td>
<td>8.1 [3.5–12.7]**</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as n or mean (95% CI), unless otherwise stated. Change of lung function was adjusted using linear regression models, with forced expiratory volume in 1 s (FEV1) or forced vital capacity (FVC) change as dependent variables, sex, age, height and disease status as independent variables, and a random intercept term for European Community Respiratory Health Survey (ECRHS) centre and sample. A negative value represents lung function decline. Prevalence of hospital admissions for breathing problems was adjusted using a logistic regression model, with hospital/ER admissions as dependent variables, sex, age and disease status as independent variables, and a random intercept term for ECRHS centre and sample. ACOS: asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome; AHR: airway hyperresponsiveness. *: refers to the comparison across the groups; #: present if a subject answered positively to one or both of "Since the last survey, have you spent a night in hospital?" "Have you visited a hospital casualty department or ER because of breathing problems?"; *: p<0.05; **: p<0.01; ***: p<0.001 for the comparison of the disease group with the "healthy" category.
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 sensitisation, 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 as asthmatics and COPD patients. Subjects with ACOS also had the same prevalence of sensitisation, allergic rhinitis and eczema with asthma. Almost all of them (92.1%) had AHR. This suggests a more severe subgroup than other asthma and COPD patients. 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 recognised 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 the Global Initiative for Asthma and the Global Initiative for Chronic Obstructive Lung Disease [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 versus asthma (or ACOS versus COPD) did not depend on the definitions used, but they reflected peculiarities of ACOS compared to asthma or COPD alone.

Change in lung function and risk of hospitalisation
While COPD is characterised 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 % pred at baseline, had a rate of hospital/ER admissions for breathing problems
during the follow-up that was more than double that of subjects with either disease alone. Indeed, asthma
with fixed airflow obstruction is one of the main clinical phenotypes of uncontrolled severe asthma [36],
characterised 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**

As in many other large-scale surveys started in the 1990s, post-bronchodilator spirometry was not
available. As a consequence, some asthmatic subjects with fully reversible obstruction could have been
false classified as COPD. To minimise this bias, we used chronic airflow obstruction (pre-bronchodilator
FEV1/FVC<LLN in both studies, 9 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 (online supplementary table S1). 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
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 aim of the study 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. However, as a
consequence of the random sampling of the population participating at ECRHS stage 1, the subjects from
the disease groups investigated are representative of the disease in the population.

Unfortunately, information on inflammatory markers to characterise 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, ACOS represents a form of
severe asthma, characterised 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.
References

