The coexistence of asthma and COPD: risk factors, clinical history and lung function trajectories

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Shareable abstract (@ERSpublications)
The coexistence of asthma and COPD is generally diagnosed in older persons. Nonetheless, prevention of this condition should start in childhood. As a priority, maternal and personal smoking avoidance should be encouraged. https://bit.ly/3uQCmIX

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Abstract

Patients with concomitant features of asthma and chronic obstructive pulmonary disease (COPD) have a heavy disease burden.

Using data collected prospectively in the European Community Respiratory Health Survey, we compared the risk factors, clinical history and lung function trajectories from early adulthood to late sixties of middle-aged subjects with asthma+COPD (n=179), past (n=263) or current (n=808) asthma alone, COPD alone (n=111) or none of these (n=3477).

Interview data and pre-bronchodilator forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were obtained during three clinical examinations in 1991–1993, 1999–2002 and 2010–2013. Disease status was classified in 2010–2013, when the subjects were aged 40–68 years, according to the presence of fixed airflow obstruction (post-bronchodilator FEV_1/FVC below the lower limit of normal), a lifetime history of asthma and cumulative exposure to tobacco or occupational inhalants. Previous lung function trajectories, clinical characteristics and risk factors of these phenotypes were estimated.

Subjects with asthma+COPD reported maternal smoking (28.2%) and respiratory infections in childhood (19.1%) more frequently than subjects with COPD alone (20.9% and 14.0%, respectively). Subjects with asthma+COPD had an impairment of lung function at age 20 years that tracked over adulthood, and more

than half of them had asthma onset in childhood. Subjects with COPD alone had the highest lifelong exposure to tobacco smoking and occupational inhalants, and they showed accelerated lung function decline during adult life.

The coexistence between asthma and COPD seems to have its origins earlier in life compared to COPD alone. These findings suggest that prevention of this severe condition, which is typical at older ages, should start in childhood.

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are common chronic respiratory diseases in the general population. Distinguishing between these conditions can be problematic, especially among older adults [1]. In fact, some patients with asthma, in particular smokers, develop fixed airflow obstruction and COPD at older ages [2]. Some patients with COPD show clinical features that are commonly observed in asthma, such as airway hyperresponsiveness (AHR), bronchodilator responsiveness (BDR) and increased eosinophils in blood and airways [3], although the development of asthma is less common among these patients.

In 1995, the American Thoracic Society (ATS) guidelines proposed a non-proportional Venn diagram to describe the overlap of chronic bronchitis, emphysema and asthma [4], and later studies quantified the extension of the overlap [5]. There is growing consensus that the widely used label "asthma–COPD overlap" encompasses heterogeneous phenotypes rather than indicating a stand-alone disease entity [6–10]. The 2020 update of the Global Initiative for Chronic Obstructive Lung Diseases (GOLD) guidelines no longer uses the asthma–COPD overlap label, and the Global Initiative for Asthma (GINA) guidelines replaced it with "asthma+COPD" [2, 3].

Owing to the rising trends in asthma incidence over the last decades [11], and the global increase in life expectancy that is shifting the age of the asthma population upwards [1], the clinical presentation of patients with both asthma and COPD has been increasing. According to a recent meta-analysis, the estimated global prevalence of asthma+COPD is 2.0%, despite large heterogeneity across studies, while the corresponding figures for asthma and COPD alone are 6.2% and 4.9%, respectively [12]. Diagnosis and clinical management of patients with asthma+COPD are challenging, because there is no consensus on how to define this condition [13], and most of the evidence regarding treatment has been extrapolated from trials on patients with either disease alone [7].

Understanding when the risk factors and clinical characteristics of asthma+COPD occur during life can help to identify susceptibility windows when prevention can be more effective [10]. Another important question is whether lung function trajectories associated with these phenotypes vary [7]. While the clinical guidelines state that patients with asthma+COPD have accelerated lung function decline compared to having COPD alone [3], a number of recent studies would question this assumption [14–20].

Given the above knowledge gaps, we classified subjects with asthma alone, COPD alone and asthma+COPD among participants in the third wave of the European Community Respiratory Health Survey (ECRHS) aged 40–68 years. We estimated the risk factors, clinical characteristics and lung function trajectories of these phenotypes in the age range 20–68 years.

Methods

Study population

ECRHS is an international cohort study on subjects from the general population aged 20–44 years at enrolment in 1991–1993 [21]. At ECRHS I, a 20% random sample of participants in a postal screening (stage 1) was invited to take part in a clinical assessment (stage 2), along with a sample enriched for subjects with respiratory symptoms. Participants in stage 2 were surveyed again in 1999–2002 at ECRHS II [22] and in 2010–2013 at ECRHS III [23], after a median follow-up time of 9 years (range 4–12 years) and 20 years (range 18–23 years), respectively. Ethical approval was obtained for each centre, and written informed consent was obtained from participants.

Clinical data

At each examination, subjects underwent standardised interviews and pre-bronchodilator spirometry (appendix E1). The maximum forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) repeatable to 150 mL were obtained [24]. Serum levels of total and specific IgE for house dust mite, timothy grass and cat allergens were also measured. At ECRHS I and II, methacholine challenge tests were performed [25]. At ECRHS III, post-bronchodilator spirometry using 200 µg salbutamol (two puffs, dose of 100 µg per puff) was conducted, and fractional exhaled nitric oxide (F_{ENO}) was determined with an

electrochemical analyser (NIOX MINO; Aerocrine AB, Solna, Sweden) at an expiratory flow rate of 50 mL·s^{-1} [26].

Definitions

We defined a lifetime history of asthma either as self-reported asthma at ECRHS I, II and/or III; or having AHR in combination with asthma-like symptoms or use of inhaled or oral respiratory medication at ECRHS I and/or II (supplementary table E1). We reconstructed lifetime occupational exposures to vapours, gas, dusts or fumes as described in appendix E1 [27]. We identified the following GOLD-defined key indicators for considering a diagnosis of COPD at ECHRS III [3]: 1) a lifetime history of exposures based on cumulative data from any time point ($\geqslant$10 pack-years smoked or $\geqslant$5 years of low-intensity exposure to occupational agents); 2) key symptoms at ECHRS III (chronic cough, chronic sputum production, dyspnoea or shortness of breath following strenuous activity); 3) early-life risk factors (respiratory infections before age of 5 years or parent had chronic bronchitis, emphysema or COPD).

Disease classification

We assigned subjects to five mutually exclusive groups at the last examination (ECRHS III), when post-bronchodilator lung function measurements were available (supplementary figure E1). All the criteria composing disease definitions were fulfilled at the time of ECRHS III on the basis of data measured at ECRHS III (lung function data, symptoms) or cumulative/past data (history of exposures, history of asthma, early-life respiratory infections). Disease groups were classified as follows: 1) asthma+COPD, defined as post-bronchodilator $FEV_1/FVC<$lower limit of normal (LLN) [28] + at least one GOLD-defined indicator for COPD (lifetime history of exposures, key symptoms and/or early life risk factors) + either lifetime asthma history or marked BDR (increase in $FEV_1>$12% and >400 mL) [2]; 2) COPD alone, defined as post-bronchodilator $FEV_1/FVC<$LLN + at least one GOLD-defined indicator for COPD + neither lifetime asthma history nor marked BDR; 3) current asthma alone, defined as lifetime asthma history + one among asthma-like symptoms, asthma attacks and use of inhaled/oral respiratory medicines in the last 12 months (with or without post-bronchodilator $FEV_1/FVC<$LLN); 4) past asthma alone, defined as lifetime asthma history but no symptoms, attacks or medication (with or without post-bronchodilator $FEV_1/FVC<$LLN); and 5) reference subjects, defined as none of the aforementioned conditions and post-bronchodilator $FEV_1/FVC\geqslant$LLN.

We excluded 18 subjects with post-bronchodilator $FEV_1/FVC<$LLN at ECRHS III who could not be classified in any of the disease groups (no GOLD-defined indicators, no asthma history) (figure 1).

Statistical analysis

For the subjects classified in disease groups at ECRHS III (age 40–68 years), we described the distribution of characteristics using mean±SD, median (Q1–Q3) or number (%), and tested overall differences across the groups using Kruskal–Wallis or Chi-squared/exact tests as appropriate. We then estimated adult-life trajectories of these phenotypes from the minimum age of 20 years at ECRHS I to the maximum age of 68 years at ECRHS III. We modelled indicators that were available for all the three time points, including two risk factors (proportion exposed to active or passive smoking), two self-reported outcomes (proportion reporting dyspnoea (ever having trouble with breathing) or medical examinations (seen by a general practitioner/specialist in the last 12 months, supplementary table E2)); and three lung function outcomes (average FEV_1 (L), FVC (L) and % FEV_1/FVC). We used generalised estimating equations with Poisson outcome distribution and log link function for binary outcomes, or a Gaussian outcome distribution and identity link function for quantitative outcomes. The models included a robust variance estimator and the following independent variables: sex, age, disease status, disease status×age (interaction term), ECRHS sample (random *versus* symptomatic), spirometer type (only for lung function outcomes) and height (only for FEV_1 and FVC). Age^2 and disease status×age^2 were also tested sequentially and included to account for non-linearity in trajectories if they improved model fitting (α=0.10). We set unstructured within-subject correlations to account for repeated measurements. We deleted missing data on adjustment variables list-wise. Each subject contributed available information from any time point. We used STATA software, release 16.1 (StataCorp, College Station, TX, USA).

Sensitivity analyses

We also estimated lung function trajectories: 1) modelling FEV_1 and FVC % predicted; 2) only considering subjects with three valid lung function measurements; and 3) after excluding subjects with post-bronchodilator $FEV_1/FVC>$LLN in combination with FEV_1 or FVC<LLN at ECRHS III, an indicator of preserved ratio impaired spirometry (PRISm) (measurements of total lung capacity and residual volume were not available). Moreover, 4) we replicated the analyses after applying disease definitions based on the GOLD fixed cut-off for persistent obstruction ($FEV_1/FVC<$0.70) (appendix E1).
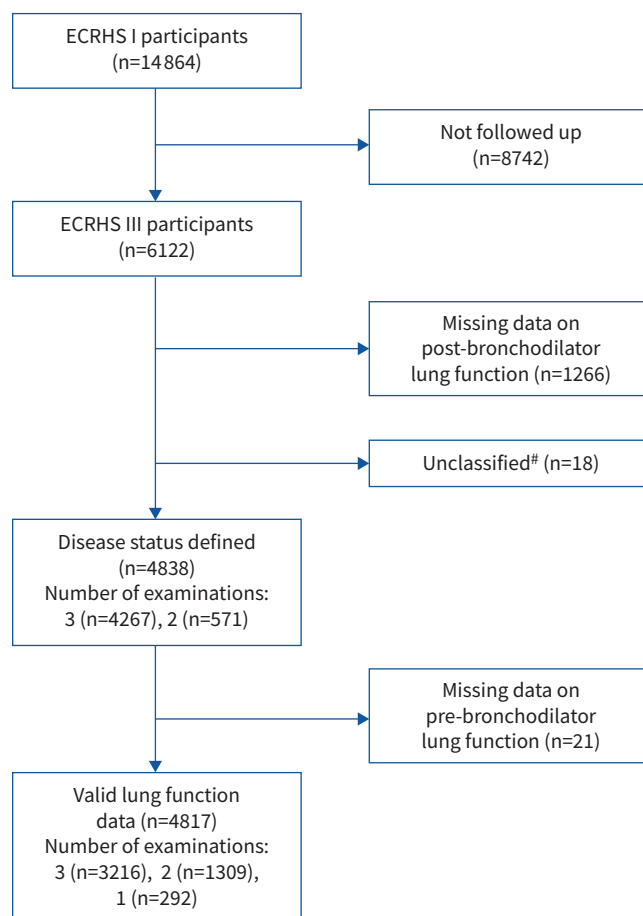
FIGURE 1 Study flowchart. #: subjects with post-bronchodilator forced expiratory volume in 1 s/forced vital capacity <lower limit of normal at European Community Respiratory Health Survey III who could not be classified in any of the disease groups (no Global Initiative for Chronic Obstructive Lung Diseases-defined indicators, no asthma history).

Results

There were 14 864, 9251 and 6122 participants, respectively, in ECRHS I, II and III who underwent clinical examinations, from 23 centres (supplementary table E3). The median time intervals between ECRHS I and II and between ECRHS II and III were 8.8 years (range 4.3–11.7 years) and 11.5 years (range 8.5–15.6 years), respectively. Compared to ECRHS I participants, the subjects followed up at ECRHS III were on average older at baseline (34.3 versus 33.6 years), less likely to have a low level of education (12.4% versus 15.8%), less likely to be current smokers (20.5% versus 23.4%) and had higher FEV_1 (99.6% versus 98.8% predicted) (supplementary table E4). Disease status was classified at ECRHS III for 4838 individuals (figure 1), of whom 4267 attended all three examinations, and 3216 had valid lung function measurements at three time points. Subjects assigned to disease groups had similar characteristics compared to the larger sample of ECRHS III participants (supplementary table E4). There were 295 subjects with a post-bronchodilator $FEV_1/FVC<LLN$; of these, 290 fulfilled at least one GOLD-defined indicator of COPD (supplementary table E5), and five were classified as having past (n=1) or current (n=4) asthma alone. There were 1248 subjects with a lifetime history of asthma, of whom 1045 reported having ever had asthma at ECRHS I, II and/or III.

Characteristics of participants at disease classification (ECRHS III)

At ECRHS III, the proportion of women in the asthma+COPD group was similar to the reference group (~50%), and intermediate between COPD (42.3%) and past/current asthma alone (>60%) (table 1). A low education level was more common in the asthma+COPD group. Obesity was more frequent among subjects with current asthma alone (31.9%) and asthma+COPD (27.7%) than with COPD alone (18.9%).

TABLE 1 Participants' characteristics at the time of disease classification (ECRHS III)

	Reference subjects	Past asthma alone	Current asthma alone	Asthma+COPD	COPD alone	Overall p-value
Subjects n	3477	263	808	179	111	
Female sex	1763/3477 (50.7)	167/263 (63.5)	492/808 (60.9)	89/179 (49.7)	47/111 (42.3)	<0.001
Age years	54.1±7.1	54.1±7.1	54.1±7.1	54.5±7.0	55.3±6.5	0.578
Low education level (completed before age 16)	375/3473 (10.8)	40/262 (15.3)	115/805 (14.3)	34/178 (19.1)	18/110 (16.4)	<0.001
BMI kg·m^{-2}	27.0± 4.7	27.0±4.8	28.2±5.6	27.4±5.3	26.5±5.2	<0.001
Obesity (BMI⩾30 kg·m^{-2})	764/3456 (22.1)	56/263 (21.3)	256/802 (31.9)	49/177 (27.7)	21/111 (18.9)	<0.001
Physical activity (exercising for ⩾1 h and ⩾2 times a week)	1483/3459 (42.9)	127/262 (48.5)	345/802 (43.0)	75/176 (42.6)	34/111 (30.6)	0.038
Post-bronchodilator FEV_1<LLN	120/3477 (3.4)	10/263 (3.8)	67/808 (8.3)	96/179 (53.6)	41/111 (36.9)	<0.001[#]
Post-bronchodilator FVC<LLN	139/3477 (4.0)	6/263 (2.3)	60/808 (7.4)	27/179 (15.1)	7/111 (6.3)	<0.001
BDR mL	57.5 (-8.8–129.4)	99.7 (14.4–172.6)	92.6 (21.6–171.6)	126.9 (48.8–236.9)	103.8 (17.8–176.9)	<0.001[#]
BDR %	1.9 (-0.3–4.2)	3.5 (0.6–6.4)	3.5 (0.8–6.6)	5.9 (2.0–12.7)	4.0 (0.9–7.2)	<0.001[#]
BDR>12% and >200 mL	71/3385 (2.1)	10/258 (3.9)	53/788 (6.7)	43/177 (24.3)	11/108 (10.2)	<0.001[#]
Marked BDR>12% and >400 mL	25/3385 (0.7)	1/258 (0.4)	19/788 (2.4)	19/177 (10.7)	-[¶]	<0.001[#]
F_{ENO} ppb						
Non-current smokers	18.0 (13.0–25.0)	18.0 (13.0–27.0)	21.0 (14.0–33.0)	22.0 (13.0–35.0)	17.5 (14.0–25.0)	<0.001
Current smokers	11.0 (8.0–16.0)	14.0 (11.0–19.0)	11.0 (8.0–16.0)	9.5 (6.0–13.0)	11.0 (7.0–16.0)	0.008
F_{ENO} ⩾25 ppb						
Non-current smokers	691/2728 (25.3)	60/221 (27.2)	254/650 (39.1)	52/127 (40.9)	13/46 (28.3)	<0.001
Current smokers	51/566 (9.0)	4/29 (13.8)	14/128 (10.9)	32/46 (6.5)	7/62 (11.3)	0.774
Childhood asthma onset (<18 years)[+]	-[¶]	75/182 (41.2)	258/672 (38.4)	79/148 (53.4)	-[¶]	0.004
Late asthma onset (>40 years)[+]	-[¶]	22/182 (12.1)	113/672 (16.8)	16/148 (10.8)	-[¶]	0.084
Asthma-like symptoms[§], last 12 months	1106/3413 (32.4)	-[¶]	719/806 (89.2)	153/177 (86.4)	75/111 (67.6)	<0.001
Key COPD symptoms[f], last 12 months	1001/3398 (29.5)	39/256 (15.2)	631/801 (78.8)	151/175 (86.3)	63/111 (56.8)	<0.001[#]
Chronic cough/sputum production	347/3426 (10.1)	15/259 (5.8)	209/792 (26.4)	62/173 (35.8)	27/110 (24.6)	<0.001[#]
MRC dyspnoea score>1	506/2753 (18.4)	31/214 (14.5)	223/630 (35.4)	56/143 (39.2)	38/85 (44.7)	<0.001
Hay fever	921/3462 (26.6)	125/262 (47.7)	471/803 (58.7)	93/178 (52.3)	17/111 (15.3)	<0.001
Eczema, ever	1327/3456 (38.4)	123/262 (47.0)	466/803 (58.0)	93/176 (52.8)	42/110 (38.2)	<0.001
Allergic sensitisation[##]	638/3316 (19.2)	109/251 (43.4)	376/771 (48.8)	80/171 (46.8)	20/107 (18.7)	<0.001
Total serum IgE kU·L^{-1}	24.5 (10.2–59.9)	30.2 (11.8–69.0)	45.5 (17.4–118.7)	72.6 (21.7–193.1)	29.7 (12.0–72.7)	<0.001
Cat owner	712/3468 (20.5)	51/262 (19.5)	141/805 (17.5)	30/177 (17.0)	19/111 (17.1)	0.263
Dog owner	652/3465 (18.8)	49/262 (18.7)	181/806 (22.5)	47/178 (26.4)	15/110 (13.6)	0.01
Mould in the house, ever	724/3429 (21.1)	43/260 (16.5)	209/792 (26.4)	32/176 (18.2)	29/110 (26.4)	0.001
Mould in the house, last 12 months	499/3426 (14.6)	27/258 (10.5)	136/786 (17.3)	21/176 (11.9)	21/110 (19.1)	0.031
Emergency room/hospital admission for breathing problems since the last survey	131/3451 (3.8)	15/261 (5.8)	101/805 (12.6)	38/177 (21.5)	4/110 (3.6)	<0.001
Heart disease (angina, heart attack, coronary heart disease)	96/3448 (2.8)	5/261 (1.9)	36/804 (4.5)	6/175 (3.4)	8/111 (7.2)	0.009

Data are presented as n/N with available data (%), mean±SD or median (Q1–Q3), unless otherwise indicated. COPD: chronic obstructive pulmonary disease; BMI: body mass index; FEV_1: forced expiratory volume in 1 s; LLN: lower limit of normal; FVC: forced vital capacity; BDR: bronchodilator responsiveness; F_{ENO}: fractional exhaled nitric oxide; MRC: Medical Research Council. [#]: this characteristic (or a closely related one) was considered for disease definition; [¶]: 0% frequency forced by disease definitions; [+]: information on age at first asthma attack was only collected for subjects who reported to have ever had asthma; [§]: wheeze, nocturnal chest tightness, breathlessness after activity/at rest/at night-time; [f]: chronic cough, chronic sputum production, dyspnoea, shortness of breath following strenuous activity; [##]: having specific IgE >0.35 kU·L^{-1} for at least one of house dust mite, timothy grass or cat allergens.

The subjects with asthma+COPD were as physically active as the subjects with current asthma alone (~43%) and more active than the COPD group (30.6%). Among non-smokers, F_{ENO} levels were highest in the group with asthma+COPD, whereas among smokers the highest level was seen in subjects with past asthma. A lifetime history of asthma was reported by 177 of the subjects with asthma+COPD (98.9%). Subjects with asthma+COPD were more likely to report a childhood asthma onset (53.4%) than subjects with past or current asthma alone (41.2% and 38.4%, respectively), and less likely to report a late asthma onset (10.8% versus 12.1% and 16.8%, respectively). Both asthma-like symptoms and GOLD-defined key COPD symptoms were more frequent among subjects with asthma+COPD than among subjects with COPD alone. Allergic outcomes were more common among subjects with the asthmatic phenotypes compared to COPD alone or reference subjects, while total serum IgE levels were highest in the group with asthma+COPD. Emergency room or hospital admissions for breathing problems were most frequent in subjects with asthma+COPD. Subjects with asthma+COPD were more likely to report use of inhaled or oral respiratory medication (72.9%) than subjects with current asthma (61.2%) or COPD alone (10.8%) at ECRHS III, but also at the other examinations (supplementary table E6).

Childhood and lifelong characteristics of participants

Subjects with asthma+COPD most frequently reported maternal smoking in childhood (28.2%), followed by those with past asthma and current asthma alone (table 2). Subjects with asthma+COPD were more likely to have parents with asthma (25.3%) or respiratory infections in childhood (19.1%) and less likely to have parents with COPD (28.7%) than subjects with COPD alone (20.8%, 14.0% and 34.3%, respectively). Lifelong cumulative exposure to tobacco smoking or occupational inhalants was lower among subjects with asthma+COPD than COPD alone. Subjects with asthma+COPD were most likely to have a history of AHR (89.6%) and high total serum IgE (73.3%).

Adult-life trajectories

In the group with asthma+COPD, the lifetime prevalence of active smoking from age 20 to 68 years was midway between the subjects with COPD and the other less exposed groups (figure 2a). We estimated a monotonic age-related decline in the proportion of smokers for all groups except for COPD, in which it reached the maximum around age 30 years before declining. The proportion of subjects exposed to passive smoking was similar between the disease groups during early adulthood (60–70%), and then it followed trajectories similar to those of active smoking at older ages (figure 2b).

No statistically significant variation in the prevalence of dyspnoea was found with ageing, except for a decrease among subjects with past asthma alone, consistent with their inactive disease status at ECRHS III

TABLE 2 Early-life and lifelong exposure to risk factors and clinical characteristics						
	Reference subjects	Past asthma alone	Current asthma alone	Asthma+ COPD	COPD alone	Overall p-value
Subjects n	3477	263	808	179	111	
Respiratory infections in childhood	287/3287 (8.7)	40/250 (16.0)	134/747 (17.9)	31/162 (19.1)	15/107 (14.0)	<0.001[#]
Maternal smoking in childhood	725/3440 (21.1)	69/260 (26.5)	203/794 (25.6)	49/174 (28.2)	23/110 (20.9)	0.007
Cat in childhood	1581/3471 (45.6)	113/263 (43.0)	367/805 (45.6)	80/177 (45.2)	58/111 (52.3)	0.604
Dog in childhood	1495/3473 (43.1)	105/263 (39.9)	356/805 (44.2)	77/177 (43.5)	46/111 (41.4)	0.803
Parental asthma	302/3235 (9.3)	48/248 (19.4)	190/754 (25.2)	40/158 (25.3)	21/101 (20.8)	<0.001
Parental COPD	589/3157 (18.7)	47/243 (19.3)	189/735 (25.7)	45/157 (28.7)	34/99 (34.3)	<0.001[#]
History of heavy smoking	1046/2713 (38.6)	69/213 (32.4)	238/672 (35.4)	71/136 (52.2)	67/83 (80.7)	<0.001[#]
History of occupational exposures	1286/3286 (39.1)	101/250 (40.4)	302/767 (39.4)	71/157 (45.2)	54/100 (54.0)	0.026[#]
History of AHR[¶]	146/2006 (7.3)	137/205 (66.8)	422/596 (70.8)	103/115 (89.6)	7/48 (14.6)	<0.001[#]
History of high total IgE[+]	924/2601 (35.5)	106/216 (49.1)	394/665 (59.3)	107/146 (73.3)	33/82 (40.2)	<0.001
History of allergic sensitisation[§]	1052/2638 (39.9)	142/228 (62.3)	484/689 (70.3)	105/150 (70.0)	32/87 (36.8)	<0.001

Data are presented as n/N with available data (%), unless otherwise indicated. COPD: chronic obstructive pulmonary disease; AHR: airway hyperresponsiveness; ECRHS: European Community Respiratory Health Survey. [#]: this characteristic (or a closely related one) was considered for disease definition; [¶]: having a 20% decrease of forced expiratory volume in 1 s at a methacholine dose ⩽1 mg at ECRHS I and/or II; [+]: having total IgE >100 kU·L^{-1} at ECRHS I, II and/or III; [§]: having specific IgE >0.35 kU·L^{-1} for at least one among house dust mite, timothy grass and cat allergens at ECRHS I, II and/or III.
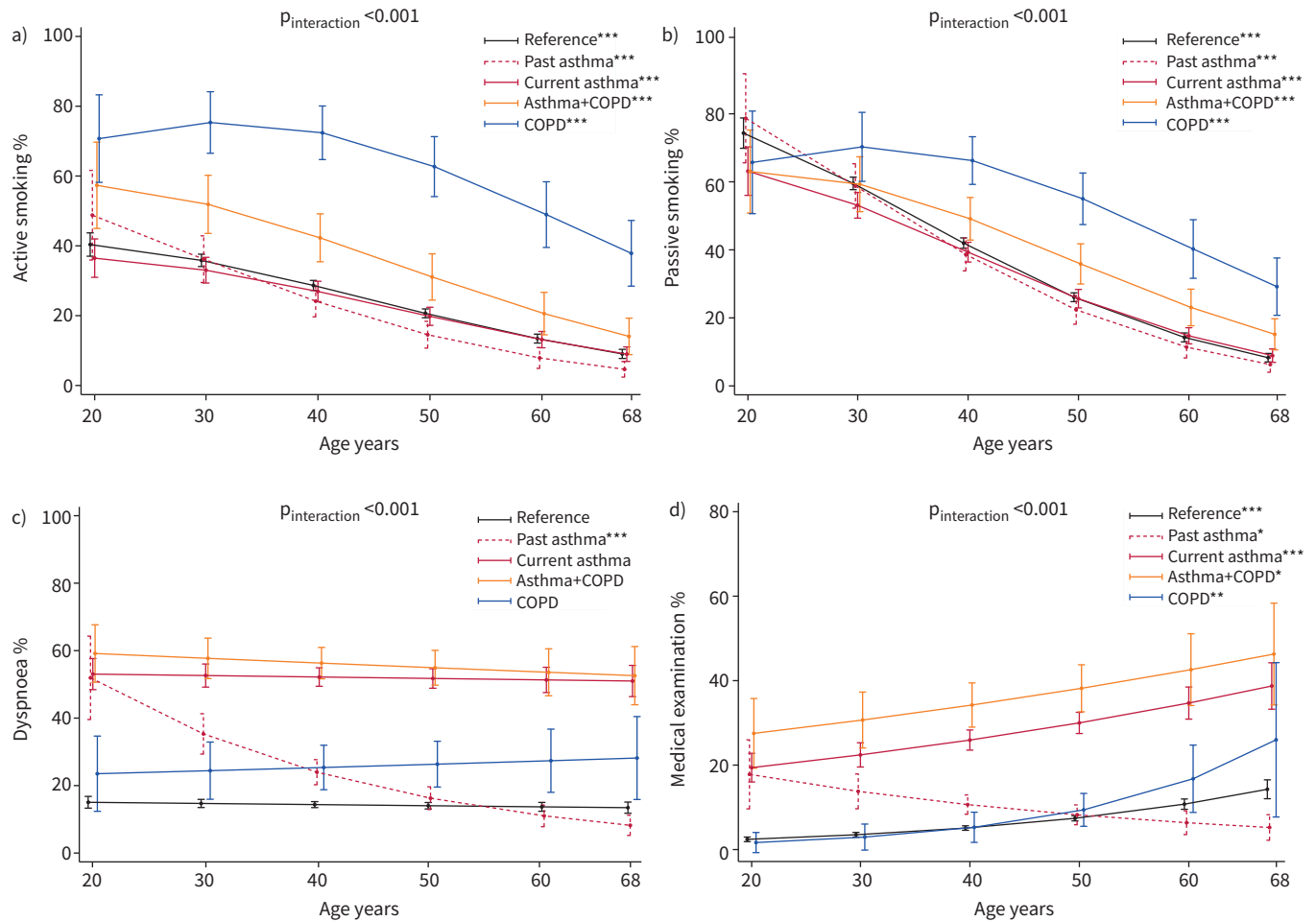
FIGURE 2 Predicted trajectories for the proportion of subjects reporting a) active smoking, b) passive smoking, c) dyspnoea or d) having been seen by a physician during the last 12 months as a function of disease group and age. Number of subjects contributing data=4838. $p_{interaction}$ obtained by Wald test (null hypothesis: true trajectories do not vary by disease group). The vertical lines represent 95% confidence intervals. Quantitative/indicator independent variables were set equal to the mean/proportion calculated over the set of subjects included. p-values are for the test of significance of the age-related trend within a disease group (null hypothesis: true proportion is constant across ages). *: p<0.05; **: p<0.01; ***: p<0.001.

(figure 2c). All groups except for past asthma showed an age-related increase in the proportion of subjects seen by a physician in the previous 12 months, which became steeper after age 50 years in the group with COPD alone (figure 2d).

Subjects with asthma+COPD had a low lung function when they were young adults, and this condition tracked over their adult lives (supplementary table E6 and figure 3). Their raw FEV_1 decline was only slightly faster than that in the current asthma alone and reference groups, whereas a steeper decline was observed for FEV_1 % predicted (supplementary figure E3a); raw FVC (figure 3b), FVC % predicted (supplementary figure E3b) and FEV_1/FVC (figure 3c) were also accelerated.

We observed the steepest rate of FEV_1 decline in subjects with COPD alone (figure 3a and supplementary figure E3a). Their FEV_1/FVC was midway between those in the asthma+COPD group and other groups during young adulthood, but then it declined steeply and reached the low level observed in asthma+COPD during the seventh decade of life (figure 3c).

Results of the sensitivity analyses were consistent with those from the main analyses (appendix E1, supplementary figures E4–E7, supplementary tables E7, E8).
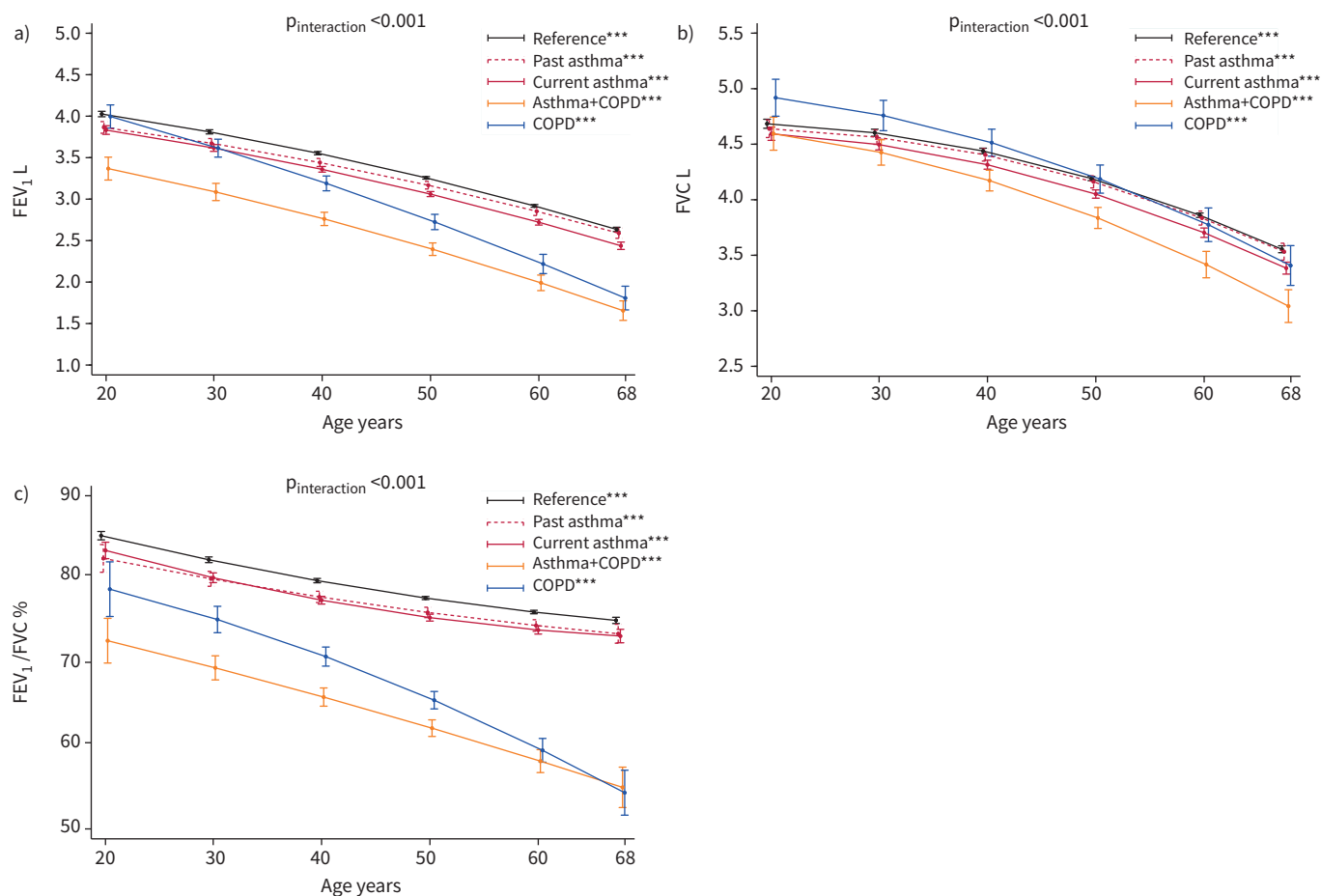
FIGURE 3 Predicted trajectories for mean pre-bronchodilator a) forced expiratory volume in 1 s (FEV_1), b) forced vital capacity (FVC) and c) FEV_1/FVC ratio as a function of disease group and age. Number of subjects contributing data=4831 (FEV_1), 4822 (FVC) and 4816 (FEV_1/FVC). $p_{interaction}$ obtained by Wald test (null hypothesis: true trajectories do not vary by disease group). The vertical lines represent 95% confidence intervals. Spirometer type was set to NDD EasyOne; quantitative/indicator independent variables were set equal to the mean/proportion calculated over the set of subjects included. ***: $p < 0.001$ for the test of significance of the age-related trend within a disease group (null hypothesis: true mean is constant across ages).

Discussion

Using data collected prospectively over 20 years from population samples, we found that subjects with both asthma and COPD at age 40–68 years were more likely to report maternal smoking and respiratory infections in childhood, but less likely to have been exposed to tobacco smoking and occupational inhalants during adult life compared to subjects with COPD alone. Estimated past trajectories of FEV_1, FVC and FEV_1/FVC ratio suggested that low lung function in young adulthood is more frequently observed among subjects who will be identified as having both asthma and COPD later in life, rather than COPD alone. However, a steep lung function decline is more common among adults who will subsequently be diagnosed with COPD alone. We hypothesise that early-life risk factors have a more prominent role in the development of asthma+COPD, whereas exposures during adult life could be stronger risk factors for the development of COPD that does not have features of asthma.

Disease classification and socio-demographics

At disease classification, all the participants in our study were ⩾40 years, an age when the overlap between asthma and COPD generally starts to be considered as a potential diagnosis [8]. The number of subjects with COPD alone was relatively small compared to the number with asthma+COPD, possibly because the age

range at ECRHS III still included a small proportion of older people, but also owing to the ECRHS design, which over-represented people with asthma [21]. The greater representation of women in the asthma+COPD group (49.7%) compared to COPD alone (42.3%) is common to several studies [15, 18, 29, 30], and consistent with the higher risk of adult asthma in women, and with the greater tobacco exposure among men in Europe [31].

Having at least one GOLD-defined indicator of COPD was an inclusion criterion for both asthma+COPD and COPD alone [3]. However, four subjects with a post-bronchodilator $FEV_1/FVC<LLN$ did not have any of these indicators. We found that GOLD-defined key symptoms of COPD and early-life respiratory infections were not very specific for COPD alone.

A lifetime history of asthma or marked BDR (increase in $FEV_1>12\%$ and >400 mL) were additional inclusion criteria for asthma+COPD, but were exclusion criteria for COPD alone [9, 32]. Nonetheless, 10.2% of subjects with COPD alone had BDR (increase in FEV_1 200–400 mL), as compared to 24.3% in asthma+COPD. Almost all subjects with asthma+COPD had a history of asthma (98.9%), which implies that only a small minority of people with persistent airflow obstruction were classified in this group based on a marked BDR alone. A marked BDR is less relevant for the diagnosis of asthma+COPD because it is infrequent [33, 34], it does not reliably differentiate between COPD with and without asthma [7], and because definitions including BDR are not stable over time [19].

Clinical characteristics of asthma+COPD at disease classification

Subjects with asthma+COPD had a prevalence of asthma-like symptoms (86.4%) and chronic cough/sputum production (35.8%) that was similar to or higher than that found in subjects with current asthma alone (89.2% and 26.4%, respectively). They were also more likely to report emergency room or hospital admissions, and they were using respiratory medication more frequently. However, subjects with asthma+COPD were as physically active as individuals with current asthma alone, suggesting a marginal impairment of their daily activities. A high degree of bronchial inflammation, as indicated by F_{ENO} levels, could be linked to the excess disease burden in subjects with asthma+COPD [35, 36]. High F_{ENO} levels are a useful marker of type-2 inflammation for asthma diagnosis, phenotyping and monitoring, and could help to predict who will benefit from inhaled corticosteroid treatment [37], but their clinical relevance in COPD and asthma+COPD is still unclear.

The early-life origins of asthma+COPD

In early adulthood, subjects with asthma+COPD had airflow obstruction (low FEV_1/FVC ratio and low FEV_1) and small lung volumes (FVC) [38], which could be explained by several, potentially concurrent, pathogenic mechanisms, including abnormal pulmonary growth and early-life insults [39]. These subjects reported the highest frequency of maternal smoking and respiratory infections during childhood, two acknowledged risk factors for reduced lung growth and lung function decline [38, 40, 41]. Subjects with asthma+COPD had a low education level, as found by others [9, 29, 42], suggesting that socio-economic deprivation could be an additional disadvantageous factor [41]. For more than half of the subjects with asthma+COPD, asthma began in childhood, which could have contributed to the development of irreversible airflow obstruction in adulthood [40, 43]. BUI et al. [20] reported that a low lung function at age 7 years is a strong risk factor for having both current asthma and COPD at age 45 years.

Adult-life trajectories

Subjects with COPD alone had the fastest rate of FEV_1 and FEV_1/FVC decline, and they reported a sharp increase in medical examinations after age 50 years, which may indicate an accelerated worsening of health with ageing compared to the other groups. Subjects with asthma+COPD had a decline in FEV_1 and FEV_1/FVC that was intermediate between COPD and the other disease groups. Overall, these findings could be explained by the higher level of exposure to inhaled pollutants in the group with COPD alone. The age-related decrease in active and passive smoking, which we observed for all the groups as a result of the successful implementation of tobacco control policies [31, 44], occurred about one life decade later for subjects with COPD alone compared to the other groups.

Lung function decline for subjects with asthma+COPD could have been mitigated by long-term anti-inflammatory treatment. Two out of three in this group had a history of allergic sensitisation or high total IgE, and sustained inhaled corticosteroid treatment could be more effective in atopic asthma [45, 46]. Almost 90% of subjects with asthma+COPD had a history of AHR, which we previously related to low lung function in young adulthood but normal subsequent FEV_1 decline in mL·year^{-1} [47].

Lung function decline in COPD with and without asthma

The finding that FEV_1 decline was faster for subjects with COPD alone than asthma+COPD is consistent with most literature [14–20], with two exceptions that could be linked to the heterogeneity captured by different disease definitions (supplementary table E9) [30, 34]. LANGE et al. [30] found a slower FEV_1 decline for subjects with early-onset asthma (age<40 years)+COPD, compared to COPD alone, but a faster decline for subjects with late-onset asthma+COPD [30]. In our study, asthma onset occurred before age 40 years for ∼90% of the subjects with asthma+COPD (table 1). At variance with our study, LANGE et al. [30] did not consider the history of smoking in the definition of asthma+COPD, whereas BDR (>200 mL after terbutaline inhalation) was an exclusion criterion for COPD alone. TKACOVA et al. [34] reported a faster FEV_1 decline among subjects with COPD and AHR compared to COPD without AHR. AHR might be related to structural airway changes and, as the authors acknowledged, its relevance as a marker of coexisting asthma is arguable [34].

Strengths and limitations

Collecting anamnestic information can be challenging for clinicians [19]. One strength of our study was having detailed information on past medical histories and risk factor exposures, collected prospectively from individual reports up to 20 years before, which plausibly reduced recall bias. The lack of objective information on early-life factors is a limitation, because these exposures were self-reported at age 20–44 years (ECRHS I). Our sample at ECRHS III derives from self-selection of participants from previous waves, under-representing younger people, smokers and subjects with a low education level or a low lung function at baseline. We used self-reported asthma rather than a more accurate clinical diagnosis for disease classification, although higher levels of bronchial inflammation and atopy in the asthma phenotypes, compared to COPD alone, indirectly supports the validity of our definitions. Another limitation is that we did not have data on blood or sputum eosinophil counts, or repeated post-bronchodilator spirometry, which could have improved disease classification [33], nor did we have data on outdoor air pollution exposure, a factor for which evidence of association with COPD incidence is still inconclusive [48, 49].

Conclusions

The coexistence of asthma and COPD seems to be a form of severe asthma with origins early in life, as opposed to COPD alone, which is more linked to adult exposures. This was suggested in our study by a greater prevalence of respiratory infections, maternal smoking and asthma during childhood, and an impairment of lung function at younger ages among subjects with asthma+COPD. These findings imply that prevention of this condition, which is typical for older adults, should start in childhood or possibly even before [50]. Public health interventions in terms of discouraging maternal smoking, promoting immunisation in childhood and preventing young people with asthma from smoking might be most effective. By contrast, COPD without concomitant features of asthma seems predominantly linked to adult-life toxic inhalant exposures. Exposure avoidance (e.g. through smoking cessation and reduction of pollution exposure in occupational settings) may be particularly beneficial against the development of the "pure COPD" phenotype, although it is also likely to reduce the transition from asthma to asthma+COPD. In our study, COPD alone seemed to have faster progression than asthma+COPD. Nonetheless, subjects with asthma+COPD are also at increased risk of developing respiratory disability, given their marked early and progressive impairment of lung function.

References

1   Postma DS, Rabe KF. The asthma-COPD overlap syndrome. *N Engl J Med* 2015; 373: 1241–1249.

2   Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2020. www.ginasthma.org Date last accessed: July 22, 2020.

3   Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management and Prevention of COPD. 2020. https://goldcopd.org/ Date last accessed: July 29, 2020.

4   American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995; 152: S77–S121.

5   Soriano JB, Davis KJ, Coleman B, *et al.* The proportional Venn diagram of obstructive lung disease: two approximations from the United States and the United Kingdom. *Chest* 2003; 124: 474–481.

6   Gibson PG, McDonald VM. Asthma-COPD overlap 2015: now we are six. *Thorax* 2015; 70: 683–691.

7   Milne S, Mannino D, Sin DD. Asthma-COPD overlap and chronic airflow obstruction: definitions, management, and unanswered questions. *J Allergy Clin Immunol Pract* 2020; 8: 483–495.

8   Bateman ED, Reddel HK, van Zyl-Smit RN, *et al.* The asthma-COPD overlap syndrome: towards a revised taxonomy of chronic airways diseases? *Lancet Respir Med* 2015; 3: 719–728.

9   Leung JM, Sin DD. Asthma-COPD overlap syndrome: pathogenesis, clinical features, and therapeutic targets. *BMJ* 2017; 358: j3772.

10 Woodruff PG, van den Berge M, Boucher RC, *et al.* American Thoracic Society/National Heart, Lung, and Blood Institute asthma-chronic obstructive pulmonary disease overlap workshop report. *Am J Respir Crit Care Med* 2017; 196: 375–381.

11 de Marco R, Cappa V, Accordini S, *et al.* Trends in the prevalence of asthma and allergic rhinitis in Italy between 1991 and 2010. *Eur Respir J* 2012; 39: 883–892.

12 Hosseini M, Almasi-Hashiani A, Sepidarkish M, *et al.* Global prevalence of asthma-COPD overlap (ACO) in the general population: a systematic review and meta-analysis. *Respir Res* 2019; 20: 229.

13 Barczyk A, Maskey-Warzechowska M, Gorska K, *et al.* Asthma-COPD overlap–a discordance between patient populations defined by different diagnostic criteria. *J Allergy Clin Immunol Pract* 2019; 7: 2326–2336.

14 de Marco R, Marcon A, Rossi A, *et al.* COPD and overlap syndrome: a longitudinal study in young European adults. *Eur Respir J* 2015; 46: 671–679.

15 Park HY, Lee SY, Kang D, *et al.* Favorable longitudinal change of lung function in patients with asthma-COPD overlap from a COPD cohort. *Respir Res* 2018; 19: 36.

16 Fu JJ, Gibson PG, Simpson JL, *et al.* Longitudinal changes in clinical outcomes in older patients with asthma, COPD and asthma-COPD overlap syndrome. *Respiration* 2014; 87: 63–74.

17 Suzuki M, Makita H, Konno S, *et al.* Asthma-like features and clinical course of chronic obstructive pulmonary disease. An analysis from the Hokkaido COPD cohort study. *Am J Respir Crit Care Med* 2016; 194: 1358–1365.

18 Hayden LP, Hardin ME, Qiu W, *et al.* Asthma is a risk factor for respiratory exacerbations without increased rate of lung function decline: five-year follow-up in adult smokers from the COPDGene Study. *Chest* 2018; 153: 368–377.

19 Barrecheguren M, Pinto L, Mostafavi-Pour-Manshadi SMY, *et al.* Identification and definition of asthma–COPD overlap: the CanCOLD study. *Respirology* 2020; 25: 836–849.

20 Bui DS, Burgess JA, Lowe AJ, *et al.* Childhood lung function predicts adult chronic obstructive pulmonary disease and asthma-chronic obstructive pulmonary disease overlap syndrome. *Am J Respir Crit Care Med* 2017; 196: 39–46.

21 Burney PG, Luczynska C, Chinn S, *et al.* The European Community Respiratory Health Survey. *Eur Respir J* 1994; 7: 954–960.

22 ECRHS II Steering Committee. The European Community Respiratory Health Survey II. *Eur Respir J* 2002; 20: 1071–1079.

23 Amaral AFS, Newson RB, Abramson MJ, *et al.* Changes in IgE sensitization and total IgE levels over 20 years of follow-up. *J Allergy Clin Immunol* 2016; 137: 1788–1795.

24 Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.

25   Chinn S, Burney P, Jarvis D, *et al.* Variation in bronchial responsiveness in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1997; 10: 2495–2501.

26   Nerpin E, Olivieri M, Gislason T, *et al.* Determinants of fractional exhaled nitric oxide in healthy men and women from the European Community Respiratory Health Survey III. *Clin Exp Allergy* 2019; 49: 969–979.

27   Lytras T, Kogevinas M, Kromhout H, *et al.* Occupational exposures and incidence of chronic bronchitis and related symptoms over two decades: the European Community Respiratory Health Survey. *Occup Environ Med* 2019; 76: 222–229.

28   Quanjer PH, Stanojevic S, Cole TJ, *et al.* Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40: 1324–1343.

29   Morgan BW, Grigsby MR, Siddharthan T, *et al.* Epidemiology and risk factors of asthma-chronic obstructive pulmonary disease overlap in low- and middle-income countries. *J Allergy Clin Immunol* 2019; 143: 1598–1606.

30   Lange P, Colak Y, Ingebrigtsen TS, *et al.* Long-term prognosis of asthma, chronic obstructive pulmonary disease, and asthma-chronic obstructive pulmonary disease overlap in the Copenhagen City Heart study: a prospective population-based analysis. *Lancet Respir Med* 2016; 4: 454–462.

31   Marcon A, Pesce G, Calciano L, *et al.* Trends in smoking initiation in Europe over 40 years: a retrospective cohort study. *PLoS One* 2018; 13: e0201881.

32   Soler-Cataluna JJ, Cosio B, Izquierdo JL, *et al.* Consensus document on the overlap phenotype COPD-asthma in COPD. *Arch Bronconeumol* 2012; 48: 331–337.

33   Miravitlles M. Diagnosis of asthma-COPD overlap: the five commandments. *Eur Respir J* 2017; 49: 1700506.

34   Tkacova R, Dai DLY, Vonk JM, *et al.* Airway hyperresponsiveness in chronic obstructive pulmonary disease: a marker of asthma-chronic obstructive pulmonary disease overlap syndrome? *J Allergy Clin Immunol* 2016; 138: 1571–1579.

35   Goto T, Camargo CA Jr, Hasegawa K. Fractional exhaled nitric oxide levels in asthma-COPD overlap syndrome: analysis of the National Health and Nutrition Examination Survey, 2007–2012. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 2149–2155.

36   Mannino DM, Gan WO, Wurst K, *et al.* Asthma and chronic obstructive pulmonary disease overlap: the effect of definitions on measures of burden. *Chronic Obstr Pulm Dis* 2017; 4: 87–96.

37   Price DB, Buhl R, Chan A, *et al.* Fractional exhaled nitric oxide as a predictor of response to inhaled corticosteroids in patients with non-specific respiratory symptoms and insignificant bronchodilator reversibility: a randomised controlled trial. *Lancet Respir Med* 2018; 6: 29–39.

38   Agusti A, Faner R. Lung function trajectories in health and disease. *Lancet Respir Med* 2019; 7: 358–364.

39   Lange P, Celli B, Agusti A, *et al.* Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med* 2015; 373: 111–122.

40   Bui DS, Lodge CJ, Burgess JA, *et al.* Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir Med* 2018; 6: 535–544.

41   Svanes C, Sunyer J, Plana E, *et al.* Early life origins of chronic obstructive pulmonary disease. *Thorax* 2010; 65: 14–20.

42   de Marco R, Pesce G, Marcon A, *et al.* The coexistence of asthma and chronic obstructive pulmonary disease (COPD): prevalence and risk factors in young, middle-aged and elderly people from the general population. *PLoS One* 2013; 8: e62985.

43   Tai A, Tran H, Roberts M, *et al.* The association between childhood asthma and adult chronic obstructive pulmonary disease. *Thorax* 2014; 69: 805–810.

44   Olivieri M, Murgia N, Carsin AE, *et al.* Effects of smoking bans on passive smoking exposure at work and at home. The European Community Respiratory Health Survey. *Indoor Air* 2019; 29: 670–679.

45   de Marco R, Marcon A, Jarvis D, *et al.* Inhaled steroids are associated with reduced lung function decline in subjects with asthma with elevated total IgE. *J Allergy Clin Immunol* 2007; 119: 611–617.

46   Marcon A, Marchetti P, Anto JM, *et al.* Atopy modifies the association between inhaled corticosteroid use and lung function decline in patients with asthma. *J Allergy Clin Immunol Pract* 2020; 8: 980–988.

47   Marcon A, Locatelli F, Keidel D, *et al.* Airway responsiveness to methacholine and incidence of COPD: an international prospective cohort study. *Thorax* 2018; 73: 825–832.

48   Schikowski T, Mills IC, Anderson HR, *et al.* Ambient air pollution: a cause of COPD? *Eur Respir J* 2014; 43: 250–263.

49   Park J, Kim HJ, Lee CH, *et al.* Impact of long-term exposure to ambient air pollution on the incidence of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Environ Res* 2021; 194: 110703.

50   Accordini S, Calciano L, Johannessen A, *et al.* A three-generation study on the association of tobacco smoking with asthma. *Int J Epidemiol* 2018; 47: 1106–1117.