ONLINE SUPPLEMENT

Title

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

Authors

Alessandro Marcon, Francesca Locatelli, Shyamali C Dharmage, Cecilie Svanes, Joachim Heinrich, Bénédicte Leynaert, Peter Burney, Angelo Corsico, Gulser Caliskan, Lucia Calciano, Thorarinn Gislason, Christer Janson, Deborah Jarvis, Rain Jõgi, Theodore Lytras, Andrei Malinovschi, Nicole Probst-Hensch, Kjell Toren, Lidia Casas, Giuseppe Verlato, Judith Garcia-Aymerich, and Simone Accordini, on behalf of the Ageing Lungs in European Cohorts (ALEC) study

Appendix E1. Supplementary information on the European Community Respiratory Health Survey

Co-ordinating center: P. Burney, S. Chinn, C. Luczynska†, D. Jarvis, E. Lai (London).

Project management group: P. Burney (Project leader-UK), S. Chinn (UK), C. Luczynska† (UK), D. Jarvis (UK), P. Vermeire† (Antwerp), H. Kesteloot (Leuven), J. Bousquet (Montpellier), D. Nowak (Hamburg), J. Prichard† (Dublin), R. de Marco† (Verona), B. Rijcken (Groningen), J.M. Anto (Barcelona), J. Alves (Oporto), G. Boman (Uppsala), N. Nielsen (Copenhagen), P. Paoletti (Pisa).

Steering Committee of ECRHS II: U. Ackermann-Liebrich (University of Basel, Switzerland); N. Kuenzli (University of Basel, and University of Southern California, Los Angeles, USA); J.M. Antó and J. Sunyer (Institut Municipal d'Investigació Médica (IMIM-IMAS), Universitat Pompeu Fabra (UPF), Spain); P. Burney (project leader), S Chinn, D. Jarvis, J. Knox and C. Luczynska† (King's College London, UK); I. Cerveri (University of Pavia, Italy); R. de Marco† (University of Verona, Italy); T. Gislason (Iceland University Hospital, Iceland); J. Heinrich and M. Wjst (GSF–Institute of Epidemiology, Germany); C. Janson (Uppsala University, Sweden); B. Leynaert and F. Neukirch (Institut National de la Sante´ et de la Recherche Medicale (INSERM), France); J. Schouten (University of Groningen, The Netherlands); C. Svanes (University of Bergen, Norway); P. Vermeire† (University of Antwerp, Belgium).

Principal investigators and senior scientific teams of ECRHS II: Australia: (M. Abramson, E.H Walters, J. Raven); Belgium: South Antwerp and Antwerp City (P. Vermeire†, J. Weyler, M. van Sprundel, V. Nelen); Estonia: Tartu (R. Jõgi, A. Soon); France: Paris (F. Neukirch, B. Leynaert, R. Liard, M. Zureik), Grenoble (I. Pin, J. Ferran-Quentin); Bordeaux (A. Taytard, C. Raherison), Montpellier (J. bBousquet, P.J. Bousquet); Germany: Erfurt (J. Heinrich, M. Wjst, C. Frye, I. Meyer); Iceland: Reykjavik (T. Gislason, E. Bjornsson, D. Gislason, K.B. Jörundsdóttir); Italy: Turin (R. Bono, M. Bugiani, P.Piccioni, E. Caria, A. Carosso, E. Migliore, G. Castiglioni), Verona (R. de Marco†, G. Verlato, E. Zanolin, S. Accordini, A. Poli, V. Lo Cascio, M. Ferrari, I. Cazzoletti), Pavia (A. Marinoni, S. Villani, M. Ponzio, F. Frigerio, M. Comelli, M. Grassi, I. Cerveri, A. Corsico); The Netherlands: Groningen and Geleen (J. Schouten, M. Kerkhof); Norway: Bergen (A. Gulsvik, E. Omenaas, C. Svanes, B. Laerum); Spain: Albacete (J. Martinez-Moratalla Rovira, E. Almar, M. Arévalo, C. Boix, G. González, J.M. Ignacio García, J. Solera, J. Damián), Galdakao (N. Muñozguren, J. Ramos, I. Urrutia, U. Aguirre), Barcelona (J.M. Antó, J. Sunyer, M. Kogevinas, J.P. Zock, X. Basagaña, A. Jaen, F. Burgos, C. Acosta), Huelva (J. Maldonado, A. Pereira, J.L. Sanchez), Oviedo (F. Payo, I. Huerta, A. de la Vega, L. Palenciano, J. Azofra, A. Cañada); Sweden: Göteborg (K. Toren, L. Lillienberg, A.C. Olin, B. Balder, A. Pfeifer-Nilsson, R. Sundberg), Umea (E. Norrman, M. Soderberg, K.A. Franklin, B. Lundback, B. Forsberg, L. Nystrom), Uppsala (C. Janson, G. Boman, D. Norback, G. Wieslander, M. Gunnbjornsdottir); Switzerland: Basel (N. Küenzli, B. Dibbert, M. Hazenkamp, M. Brutsche, U. Ackermann-Liebrich); United Kingdom: Ipswich (D. Jarvis, R. Hall, D. Seaton), Norwich (D. Jarvis, B. Harrison).

Principal Investigators and senior scientific teams of ECRHS III: Australia: Melbourne (M. Abramson, G. Benke, S. Dharmage, B. Thompson, S. Kaushik, M. Matheson); Belgium: South Antwerp & Antwerp City (J. Weyler, H. Bentouhami, V. Nelen); Denmark: Aarhus (V. Schlunssen, T. Sigsgaard, R.Dahl); Estonia: Tartu (R. Jõgi, H.Orru); France: Bordeaux (C. Raherison, P.O. Girodet), Grenoble (I. Pin, V. Siroux, J. Ferran, J.L. Cracowski), Montpellier (P. Demoly, A.Bourdin, I. Vachier), Paris (B. Leynaert, D. Soussan, D. Courbon, C. Neukirch, L. Alavoine, X. Duval, I. Poirier); Germany: Erfurt (J. Heinrich, E. Becker, G. Woelke, O. Manuwald), Hamburg (H. Magnussen, D. Nowak, A.M. Kirsten); Iceland: Reykjavik (T. Gislason, B. Benediktsdottir, D. Gislason, E.S. Arnardottir, M. Clausen, G. Gudmundsson, L. Gudmundsdottir, H. Palsdottir, K. Olafsdottir, S. Sigmundsdottir, K. Bara-Jörundsdottir); Italy: Pavia (I. Cerveri, A.Corsico, A. Grosso, F. Albicini, E. Gini, E.M. Di Vincenzo, V. Ronzoni, S. Villani, F. Campanella, M. Gnesi, F. Manzoni, L. Rossi, O. Ferraro),Turin: (M. Bugiani, R. Bono, P. Piccioni, R. Tassinari, V. Bellisario, G. Trucco), Verona: (R de Marco†, S. Accordini, L. Calciano, L. Cazzoletti, M. Ferrari, A.M. Fratta Pasini, F. Locatelli, P. Marchetti, A. Marcon, E. Montoli, G. Nguyen, M. Olivieri, C. Papadopoulou, C.Posenato, G. Pesce, P. Vallerio, G. Verlato, E. Zanolin); Netherlands: Groningen (H.M. Boezen); Norway: (C. Svanes, E. Omenaas, A. Johannessen, T. Skorge, F. Gomez Real); Spain: Albacete (J. Martinez-Moratalla Rovira, E. Almar, A. Mateos, S. García, A. Núñez, P. López, R. Sánchez, E. Mancebo), Barcelona:(J.M. Antó, J.P. Zock, J. Garcia-Aymerich, M. Kogevinas, X. Basagaña, A.E. Carsin, F. Burgos, C. Sanjuas, S. Guerra, B. Jacquemin, P. Davdand); Galdakao (N. Muñozguren, I. Urrutia, U. Aguirre, S. Pascual); Huelva (J. Antonio Maldonado, A. Pereira, J. Luis Sánchez, L. Palacios); Oviedo (F. Payo, I.

Huerta, N. Sánchez, M. Fernández, B. Robles); Sweden: Göteborg (K. Torén, M. Holm, J.L. Kim, A.C. Olin, A. Dahlman-Höglund), Umea (B. Forsberg, L. Braback, L. Modig, B. Järvholm, H. Bertilsson, K.A. Franklin, C. Wahlgreen), Uppsala:(B. Andersson, D. Norback, U. Spetz Nystrom, G. Wieslander, G.M. Bodinaa Lund, K Nisser); Switzerland: Basel (N.M. Probst-Hensch, N. Künzli, D. Stolz, C. Schindler, T. Rochat, J.M. Gaspoz, E. Zemp Stutz, M. Adam, C. Autenrieth, I. Curjuric, J. Dratva, A. Di Pasquale, R. Ducret-Stich, E. Fischer, L. Grize, A. Hensel, D. Keidel, A. Kumar, M. Imboden, N. Maire, A. Mehta, H. Phuleria, M. Ragettli, M. Ritter, E. Schaffner, G.A. Thun, A. Ineichen, T. Schikowski, M. Tarantino, M. Tsai); UK: London (P. Burney, D. Jarvis, S. Kapur, R. Newson, J. Potts), Ipswich (N. Innes), Norwich (A. Wilson).

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Appendix E2. Additional methods and results

Clinical measurements

At each of the three examinations (ECRHS I, II and III), height and weight were measured and body mass index was calculated (kg/m^2). Subjects were advised to avoid using a β_2-agonist or anticholinergic inhaler for 4 h and oral medication (β_2-agonist, theophylline or antimuscarinic) for 8 h before the clinical tests. Time since the most recent use of long-acting β_2-agonists was recorded; lung function measurements from subjects who had used long-acting β_2-agonists within the previous 12 hours were excluded (n=26 observations), to minimise bias from short-term bronchodilation effects. Biomedin or SensorMedics spirometers were used in most centres at ECRHS I and II, whereas NDD EasyOne was used in all centres at ECRHS III, see supplementary Table E1 of Marcon et al. 2018 (1).

Exposures to occupational agents

At ECRHS II and III, participants provided a detailed list of their previous and present occupations. Exposures were assessed by linking the International Classification of Occupations 88 codes of each employment to the ALOHA(+) Job Exposure Matrix, which assigns three levels of exposure (none, low, high) to 10 categories of agents. The weighted total duration of exposed jobs during the period was calculated using weights of 1 and 4 for low-exposure and high-exposure jobs, respectively (2). For the purpose of disease classification, ≥5 years low-intensity exposures (or equivalent high-intensity exposures) to occupational agents were considered as one of the criteria for COPD or asthma+COPD.

Disease definitions based on the GOLD fixed cut-off criterion

For sensitivity analysis, we also applied disease definitions based on the GOLD fixed cut-off criterion of persistent airflow obstruction ($FEV_1/FVC < 0.70$) (3), which replaced the LLN cut-off ($FEV_1/FVC < LLN$), and replicated the main analysis. We assigned subjects to 5 mutually exclusive groups at the last examination (ECRHS III). 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:

1) **Asthma+COPD** (n=247): postbronchodilator $FEV_1/FVC < 0.70$ + 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 > 400mL)
2) **COPD alone** (n=208): postbronchodilator $FEV_1/FVC < 0.70$ + at least one GOLD-defined indicator for COPD + *neither* lifetime asthma history *nor* marked BDR
3) **Current asthma alone** (n=750): lifetime asthma history + one among: asthma-like symptoms, asthma attacks, use of inhaled/oral respiratory medicines in the last 12 months (with or without postbronchodilator $FEV_1/FVC < 0.70$)
4) **Past asthma alone** (n=253): lifetime asthma history but no symptoms, attacks, or medication (with or without postbronchodilator $FEV_1/FVC < 0.70$)
5) **Reference subjects** (n=3360): none of the aforementioned conditions and postbronchodilator $FEV_1/FVC \geq 0.70$.

Results of the sensitivity analyses

Lung function trajectories were similar when considering only the subjects with three measurements available (**Figure E4**), as well as when excluding the subjects with a spirometric pattern compatible with PRISm (**Figure E5**), who were 3.8, 9.9, and 5.2% of the past asthma alone, current asthma alone and reference groups, respectively.

The results were also consistent when using disease definitions based on the GOLD criterion of obstruction (**Figures E6-E7**). However, the subjects with COPD alone were older on average (57.5 years) (**Table E7**), less likely to have smoked ≥10 pack-years, and the difference in the proportion reporting childhood respiratory infections between asthma+COPD and COPD alone became wider (22.6 and 13.4%, respectively) compared to the main analysis (19.1 and 14.0%, respectively) (**Table E8**).

Table E1

Definitions of additional covariates.

Covariate	Definition (Q = questionnaire item)	Source of information
Low education	Q32 Are you a full time student? Q32.1 At what age did you complete full time education?	ECRHS I [a]
Physical activity	Exercising with a frequency of two or more times a week ('2–3 times a week' or greater) and with a duration of about 1 hour a week or more (4), based on: Q40 How often do you usually exercise so much that you get out of breath or sweat? Q41 How many hours a week do you usually exercise so much that you get out of breath or sweat?	ECRHS III
Age at asthma onset	Q13 Have you ever had asthma? Q13.2 How old were you when you had your first attack of asthma?	ECRHS I [a]
Asthma-like symptoms, last 12 months	Q1 Have you had wheezing or whistling in your chest at any time in the last 12 months? Q2 Have you woken up with a feeling of tightness in your chest at any time in the last 12 months? Q3 Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 months? Q4 Have you had an attack of shortness of breath that came on following strenuous activity at any time in the last 12 months? Q5 Have you been woken by an attack of shortness of breath at any time in the last 12 months?	ECRHS III
Chronic cough	Q9 Do you usually cough during the day, or at night, in the winter? Q9.1 Do you cough like this on most days for as much as three months each year?	ECRHS III
Chronic sputum production	Q11 Do you usually bring up any phlegm from your chest during the day, or at night, in the winter? Q11.1 Do you bring up phlegm like this on most days for as much as three months each year?	ECRHS III
Medical Research Council dyspnoea score>1	Answer NO to: Q14 Are you disabled from walking by a condition other than heart or lung disease?	ECRHS III

	+ Answer YES to: Q14.1 Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?	
Hay fever	Q20 Do you have any nasal allergies, including hay fever?	ECRHS III
Eczema, ever	Q28 Have you ever had eczema or any kind of skin allergy?	ECRHS III
Cat owner	Q64 Do you keep a cat?	ECRHS III
Dog owner	Q65 Do you keep a dog?	ECRHS III
Mould in the house, ever	Q56 Has there ever been any mould or mildew on any surface, other than food, inside the home?	ECRHS III
Mould in the house, last 12 months	Answer YES to both: Q56 Has there ever been any mould or mildew on any surface, other than food, inside the home? Q56.1 Has there ever been any mould or mildew on any surface inside the home in the last 12 months?	ECRHS III
Respiratory infections in childhood	Q31 Did you have a serious respiratory infection before the age of five years?	ECRHS I
Maternal smoking in childhood	Q19 Did your mother ever smoke regularly during your childhood, or before you were born?	ECRHS I
Cat in childhood Dog in childhood	When you were a child did anyone in your household keep any of the following pets? Q51.1 cats Q51.2 dogs	ECRHS I
Parental asthma	Having one or both parents with asthma, based on: Q25 Did your mother ever have asthma? Q27 Did your father ever have asthma?	ECRHS I
Parental COPD	Did your biological parents ever suffer from chronic bronchitis, emphysema and/or COPD? Q35.2.1 Mother Q35.2.2 Father	ECRHS III
History of heavy smoking	Having smoked ≥10 pack-years over lifetime (5)	ECRHS III
History of occupational exposures	≥5 years of low-intensity or equivalent exposure to occupational agents (2)	ECRHS II and III
Use of respiratory medication, last 12 months	Q78 Have you used any inhaled medicines to help your breathing at any time in the last 12 months? Q79 Have you used any pills, capsules, tablets or medicines, other than inhaled medicines, to help your breathing at any time in the last 12 months?	ECRHS III
Preserved ratio impaired spirometry (PRISm)	Postbronchodilator FEV_1/FVC >LLN in combination with postbronchodilator FEV_1 <LLN or postbronchodilator FVC <LLN	ECRHS III
Emergency Room/hospital admission for breathing problems since the last survey	Answer YES to both: Q93 Since the last survey, have you visited a hospital casualty department or emergency room (for any reason, apart from accidents and injuries)? Q93.1 Was this due at least once to breathing problems? AND/OR Answer YES to both: Q94 Since the last survey, have you spent a night in hospital (for any reason, apart from accidents and injuries)? Q94.1 Was this due at least once to breathing problems?	ECRHS III
Heart disease	Q91.2.1 Do you have or have you ever had any of the following illnesses: Angina, heart attack, coronary heart disease?	ECRHS III

[a] data from ECRHS II and/or III were also used when information from ECRHS I was missing

Table E2

Definition of medical examinations (having being seen by a general practitioner or specialist at least once) in the last 12 months at ECRHS I, II, and III.

ECRHS I	ECRHS II	ECRHS III
Answer YES to Q71 Have you ever been seen by a doctor because of breathing problems or because of shortness of breath? + **Options 1, 2 or 3 of Q71.1** When was the last time you were seen by a doctor because of breathing problems or because of shortness of breath? 1) within the last seven days 2) more than seven days ago but within the last four weeks 3) more than four weeks ago but within the last 12 months 4) more than a year ago	**Answer YES to Q86** Since the last survey have you been seen by a doctor because of breathing problems or because of shortness of breath? ***+ one among:*** **Answer YES to Q86.1** Have you been seen by a general practitioner because of breathing problems or shortness of breath in the last 12 months? ***or*** **Answer YES to Q86.4** Have you seen a specialist (chest physician, allergy specialist, internal medicine specialist, ENT doctor) because of your breathing problems or shortness of breath in the last 12 months?	**Answer YES to Q95** In the last 12 months have you been seen by a general practitioner (for any reason, apart from accidents and injuries)? + **≥1 examination reported at Q95.2** How many were for breathing problems? ***or*** **Answer YES to Q96** In the last 12 months have you been seen by a specialist (for any reason, apart from accidents and injuries)? + **≥1 examination reported at Q96.2** How many times have you seen a specialist (chest physician, allergy specialist, internal medicine specialist, ENT doctor) because of breathing problems in the last 12 months?

Table E3

Number of participants in ECRHS I, II and III, and number of subjects included in the analysis, by centre and sample. [a]

Country	Centre	ECRHS I (1991–1993)	ECRHS II (1999–2002)	ECRHS III (2010–2013)	Subjects included
Belgium	Antwerp City	651	333	194	172
	Antwerp South	634	386	170	129
Estonia	Tartu	558	328	165	132
Germany	Erfurt	731	287	336	301
	Hamburg	1252	303	304	260
Spain	Albacete	626	449	244	232
	Barcelona	515	361	213	130
	Galdakao	592	443	385	313
	Huelva	403	306	156	137
	Oviedo	524	342	185	166
France	Bordeaux	544	165	206	114
	Grenoble	522	423	378	268
	Montpellier	456	202	187	122
	Paris	651	433	360	212
Italy	Pavia	310	192	77	66
Iceland	Reykjavik	647	524	453	386
Norway	Bergen	835	596	365	338
Sweden	Gothenburg	866	628	342	243
	Umea	708	543	297	230
	Uppsala	823	679	422	312
Australia	Melbourne	876	637	318	261
United Kingdom	Ipswich	559	373	182	155
	Norwich	581	318	183	159
	Random sample	*12756 (86%)*	*7786 (84%)*	*5291 (86%)*	*4170 (86%)*
	Symptomatic sample [b]	*2108 (14%)*	*1465 (16%)*	*831 (14%)*	*668 (14%)*
	Total	14864 (100%)	9251 (100%)	6122 (100%)	4838 (100%)

[a] centres excluded were: Aarhus, Denmark (did not take part in ECRHS II); Cardiff, UK and Portland, USA (did not take part in ECRHS III); Verona and Turin, Italy (did not collect post-BD lung function data); Basel, Switzerland (did not collect data on respiratory medication use).

[b] consisting of subjects who reported recent respiratory symptoms, asthma attacks, or use of asthma medication in ECRHS stage 1 (postal screening questionnaire)

Table E4

Baseline characteristics of participants in ECRHS I, II, III, and of the subsample of ECRHS III participants included in the analysis. [a]

Characteristics	ECRHS I participants	ECRHS II participants	ECRHS III participants	Subjects included
N.	14864	9251	6122	4838
Female sex	7772 (52.3)	4885 (52.8)	3243 (53.0)	2558 (52.9)
Age (year)	33.6±7.2	34.0±7.2	34.3±7.1	34.1±7.1
BMI (kg/m^2)	23.9±3.9	24.0±3.9	23.9±3.8	24.0±3.8
Low education	2323 (15.8)	1187 (12.8)	754 (12.4)	582 (12.0)
Smoking habits				
never smoker	6123 (41.2)	4047 (43.8)	2711 (44.3)	2133 (44.1)
ex-smoker	5257 (35.4)	3178 (34.4)	2156 (35.2)	1693 (35.0)
current smoker	3473 (23.4)	2024 (21.9)	1253 (20.5)	1011 (20.9)
Ever asthma	1855 (12.5)	1217 (13.2)	749 (12.3)	568 (11.8)
Allergic sensitisation				
present[b]	3789 (32.6)	2481 (32.2)	1654 (31.4)	1305 (30.9)
absent	7818 (67.4)	5221 (67.8)	3606 (68.6)	2923 (69.1)
Pre-BD FEV_1 % predicted (%)	98.8±13.3	99.2±13.1	99.6±13.1	99.6±13.0

[a] n. (%) of subjects with a characteristic or mean±SD.

[b] having specific IgE >0.35 kU/L for at least one among house-dust mite, timothy grass, or cat allergens

Table E5

Distribution of the GOLD-defined key indicators for COPD among the subjects with postbronchodilator FEV_1/FVC < LLN, asthma+COPD, or COPD alone. [a]

Key COPD indicator	Definition	Post-BD FEV_1/FVC < LLN (n=295)	Asthma+COPD (n=179)	COPD alone (n=111)
History of exposures	≥10 pack-years smoked **and/or** ≥5 years of low-intensity exposure to occupational agents	196/243 (80.7)	111/146 (76.0)	85/93 (91.4)
Symptoms at ECRHS III	chronic cough **and/or** chronic sputum production **and/or** dyspnoea **and/or** shortness of breath following strenuous activity	214/291 (73.5)	151/175 (86.3)	63/111 (56.8)
Early-life risk factors	respiratory infections before age of 5 **and/or** parent suffered from chronic bronchitis, emphysema or COPD	115/293 (39.2)	71/177 (40.1)	44/111 (39.6)
Number of indicators	none	5 (1.7%) [b]	-	-
	1	110 (37.3)	59 (33.0)	51 (46.0)
	2	125 (42.4)	86 (48.0)	39 (35.1)
	3	55 (18.6)	34 (19.0)	21 (18.9)

[a] n. of subjects with a characteristic / N. of subjects with available data (%)

[b] eventually classified as having past asthma alone (n=1) or current asthma alone (n=4)

Table E6

Prebronchodilator lung function measurements and use of respiratory medication at ECRHS I, II, and III by disease group. [a]

		Reference subjects (n=3477)	Past asthma alone (n=263)	Current asthma alone (n=808)	Asthma+COPD (n=179)	COPD alone (n=111)
Prebronchodilator FEV_1 (L)						
	ECRHS I	3.83±0.78	3.52±0.73	3.46±0.80	3.04±0.81	3.67±0.86
	ECRHS II	3.62±0.78	3.33±0.75	3.27±0.77	2.76±0.75	3.24±0.84
	ECRHS III	3.12±0.72	2.89±0.72	2.79±0.72	2.19±0.70	2.51±0.79
Prebronchodilator FVC (L)						
	ECRHS I	4.58±0.97	4.33±0.93	4.27±0.97	4.32±1.07	4.91±1.18
	ECRHS II	4.45±0.97	4.19±0.91	4.14±0.98	4.12±1.04	4.52±1.15
	ECRHS III	4.06±0.94	3.84±0.93	3.74±0.94	3.64±1.03	4.07±1.19
Prebronchodilator $\%FEV_1/FVC$						
	ECRHS I	83.8±5.9	81.6±6.4	81.1±7.4	70.2±8.3	75.6±6.4
	ECRHS II	81.6±5.4	79.7±5.6	79.2±6.6	67.0±7.4	71.7±6.3
	ECRHS III	77.1±5.0	75.5±5.2	74.9±5.6	59.8±6.8	61.5±6.3
Postbronchodilator FEV_1 (L)						
	ECRHS III	3.19±0.73	2.99±0.72	2.90±0.73	2.34±0.71	2.65±0.82
Postbronchodilator FVC (L)						
	ECRHS III	4.02±0.94	3.83±0.92	3.74±0.95	3.82±1.03	4.21±1.18
Postbronchodilator $\%FEV_1/FVC$						
	ECRHS III	79.6±4.9	78.3±4.9	77.7±5.4	61.0±6.5	62.5±5.8
Any inhaled or oral medicine for breathing problems, last 12 months						
	ECRHS I	358/3471 (10.3)	76/263 (28.9)	395/802 (49.2)	101/177 (57.1)	11/177 (9.9)
	ECRHS II	151/3027 (5.0)	65/242 (26.9)	378/731 (51.7)	98/148 (66.2)	5/92 (5.4)
	ECRHS III	176/3439 (5.1)	0/259 (0.0)	488/798 (61.2)	129/177 (72.9)	12/111 (10.8)
Short-acting β_2-agonists, last 12 months						
	ECRHS I	25/3464 (0.7)	35/261 (13.4)	256/798 (32.1)	80/174 (46.0)	0/111 (0.0)
	ECRHS II	32/3029 (1.1)	41/241 (17.0)	288/721 (39.9)	78/145 (53.8)	1/92 (1.1)
	ECRHS III	56/3452 (1.6)	0/262 (0.0)	317/740 (42.8)	80/157 (51.0)	2/107 (1.9)
ICS, last 12 months						
	ECRHS I	18/3460 (0.5)	15/254 (5.9)	110/771 (14.3)	37/168 (22.0)	0/111 (0.0)
	ECRHS II	29/3031 (1.0)	18/241 (7.5)	176/723 (24.3)	61/145 (42.1)	1/92 (1.1)

ECRHS III	47/3450 (1.4)	0/262 (0)	283/737 (38.4)	90/164 (54.9)	4/106 (3.8)
Long-acting β_2-agonists, last 12 months					
ECRHS II	2/3031 (0.1)	3/241 (1.2)	58/718 (8.1)	30/145 (20.7)	1/92 (1.1)
ECRHS III	24/3446 (0.7)	0/262 (0)	205/719 (28.5)	77/155 (49.7)	3/107 (2.8)

[a] mean±SD or n. of subjects with a characteristic / N. of subjects with available data (%).

Table E7

Participants' characteristics at the time of disease classification (ECRHS III). **Sensitivity analysis using disease definitions based on the GOLD fixed cut-off**.[a]

	Reference subjects (n=3360)	Past asthma alone (n=253)	Current asthma alone (n=750)	Asthma+COPD (n=247)	COPD alone (n=208)	Overall p-value
Female sex	1719/3360 (51.2)	162/253 (64.0)	469/750 (62.5)	117/247 (47.4)	82/208 (39.4)	<0.001
Age (years)	53.9±7.1	53.9±7.2	53.7±7.1	55.9±6.8	57.5±6.1	<0.001
Low education (completed before age 16)	367/3356 (10.9)	40/252 (15.9)	107/747 (14.3)	42/246 (17.1)	24/207 (11.6)	0.002
Body mass index	27.0±4.7	27.1±4.8	28.2±5.6	27.5±5.5	26.4±4.7	<0.001
Obesity (body mass index ≥30 kg/m^2)	742/3340 (22.2)	55/253 (21.7)	239/744 (32.1)	67/245 (27.4)	40/207 (19.3)	<0.001
Physical activity (exercising for ≥1 hour and ≥2 times a week)	1445/3343 (43.2)	124/252 (49.2)	323/744 (43.4)	100/244 (41.0)	66/207 (31.9)	0.005
BDR (mL)	56.3 (-9.4–128.2)	97.6 (15.7–167.5)	87.8 (19.4–165.0)	132.5 (50.6–241.3)	88.5 (15.0–182.5)	<0.001 [d]
BDR (%)	1.9 (-0.3–4.2)	3.5 (0.6–6.2)	3.3 (0.7–6.3)	5.9 (2.1–11.3)	3.5 (0.6–7.1)	<0.001 [d]
BDR (>12% and > 200mL)	65/3275 (2.0)	8/248 (3.2)	46/730 (6.3)	52/245 (21.2)	15/200 (7.5)	<0.001 [d]
Marked BDR (>12% and > 400mL)	25/3275 (0.8)	1/248 (0.4)	19/730 (2.6)	19/245 (7.8)	- [b]	<0.001 [d]
FeNO (ppb), non-current smokers	18.0 (13.0–25.0)	18.0 (12.0–27.0)	21.0 (14.0–32.0)	22.0 (14.0–38.0)	18.0 (14.0–26.0)	<0.001
FeNO ≥25 ppb (non-current smokers)	665/2655 (25.1)	58/213 (27.2)	230/604 (38.1)	78/181 (43.1)	33/103 (32.0)	<0.001
FeNO (ppb), current smokers	11.0 (8.0–16.0)	14.0 (11.0–20.0)	11.5 (8.0–16.0)	10.0 (6.0–13.0)	11.0 (7.0–16.0)	0.005
FeNO ≥25 ppb (current smokers)	47/528 (8.9)	4/27 (14.8)	13/120 (10.8)	4/56 (7.1)	11/97 (11.3)	0.719

Childhood asthma onset (<18 years)	- [b]	72/175 (41.2)	239/622 (38.4)	101/205 (49.3)	- [b]	0.024
Late asthma onset (>40 years)	- [b]	20/175 (11.4)	102/622 (16.4)	29/205 (14.2)	- [b]	0.246
Asthma-like symptoms, last 12 months	1058/3301 (32.1)	- [b]	670/748 (89.6)	202/245 (82.5)	119/204 (58.3)	<0.001
Key COPD symptoms, last 12 months	955/3286 (29.1)	36/246 (14.6)	581/743 (78.2)	204/243 (84.0)	109/205 (53.2)	<0.001 [d]
Chronic cough/sputum production	325/3312 (9.8)	13/249 (5.2)	194/734 (26.4)	79/241 (32.8)	49/204 (24.0)	<0.001 [d]
Medical Research Council dyspnoea score >1	488/2670 (18.3)	29/204 (14.2)	205/585 (35.0)	76/198 (38.4)	54/152 (35.5)	<0.001
Hay fever	897/3346 (26.8)	122/252 (48.4)	436/745 (58.5)	131/246 (53.3)	38/207 (18.4)	<0.001
Eczema, ever	1289/3339 (38.6)	116/252 (46.0)	437/745 (58.7)	129/244 (52.9)	76/207 (36.7)	<0.001
Allergic sensitisation [c]	625/3203 (19.5)	105/241 (43.6)	345/713 (48.4)	115/239 (48.1)	31/200 (15.5)	<0.001
Total serum IgE (kU/L)	14.5 (10.2–60.4)	31.4 (11.8–69.0)	44.5 (17.4–113.1)	76.0 (19.9–180.9)	27.4 (12.8–64.9)	<0.001
Cat owner	693/3351 (20.7)	49/252 (19.4)	132/747 (17.7)	41/245 (16.7)	32/208 (15.4)	0.099
Dog owner	637/3348 (19.0)	48/252 (19.1)	173/748 (23.1)	56/246 (22.8)	25/207 (12.1)	0.003
Mould in the house, ever	700/3313 (21.1)	41/250 (16.4)	188/734 (25.6)	55/244 (22.5)	49/206 (23.8)	0.018
Mould in the house, last 12 months	482/3310 (14.6)	25/248 (10.1)	120/729 (16.5)	39/243 (16.1)	34/206 (16.5)	0.141
Heart disease (angina, heart attack, coronary heart disease)	94/3333 (2.8)	5/251 (2.0)	32/746 (4.3)	10/243 (4.1)	10/206 (4.9)	0.086
Emergency Room/hospital admission for breathing problems since the last survey	125/3335 (3.8)	15/251 (6.0)	94/747 (12.6)	45/245 (18.4)	10/206 (4.9)	<0.001

[a] n. of subjects with a characteristic / N. of subjects with available data (%), mean±SD or median (Q1–Q3)

[b] 0% frequency forced by disease definitions

[c] having specific IgE >0.35 kU/L for at least one among house-dust mite, timothy grass, or cat allergens

[d] this characteristic (or a closely related one) was considered for disease definition

Table E8

Early-life and lifelong exposure to risk factors and clinical characteristics. **Sensitivity analysis using disease definitions based on the GOLD fixed cut-off**.[a]

	Reference subjects (n=3360)	Past asthma alone (n=253)	Current asthma alone (n=750)	Asthma+COPD (n=247)	COPD alone (n=208)	Overall p-value
Respiratory infections in childhood	275/3174 (8.7)	37/240 (15.4)	117/693 (22.6)	51/266 (22.6)	27/201 (13.4)	<0.001 [e]
Maternal smoking in childhood	698/3323 (21.0)	63/250 (25.2)	193/739 (26.1)	65/239 (27.2)	46/207 (22.2)	0.008
Cat in childhood	1514/3354 (45.1)	110/253 (43.5)	336/747 (45.0)	114/245 (46.5)	115/208 (55.3)	0.066
Dog in childhood	1446/3356 (43.1)	104/253 (41.1)	331/747 (44.3)	103/245 (42.0)	84/208 (40.4)	0.813
Parental asthma	292/3123 (9.4)	47/240 (19.6)	175/699 (25.0)	56/221 (25.3)	30/195 (15.4)	<0.001
Parental COPD	569/3058 (18.6)	45/234 (19.2)	173/678 (25.5)	63/223 (28.3)	54/182 (29.7)	<0.001 [e]
History of heavy smoking	987/2617 (37.7)	64/205 (31.2)	206/620 (33.2)	108/196 (55.1)	126/167 (75.5)	<0.001 [e]
History of occupational exposures	1238/3172 (39.0)	95/241 (39.4)	275/710 (38.7)	104/223 (46.6)	102/194 (52.6)	0.001 [e]
History of AHR [b]	134/1934 (6.9)	133/197 (67.5)	382/552 (69.2)	147/167 (88.0)	16/106 (15.1)	<0.001
History of high total IgE [c]	892/2535 (35.2)	129/212 (60.9)	412/623 (66.1)	139/204 (68.1)	63/167 (37.7)	<0.001
History of allergic sensitisation [d]	1009/2782 (36.3)	136/223 (61.0)	445/668 (66.6)	150/222 (67.6)	68/183 (37.2)	<0.001

[a] n. of subjects with a characteristic / N. of subjects with available data (%)

[b] having a 20% decrease of FEV_1 at a methacholine dose ≤1 mg at ECRHS I and/or II

[c] having total IgE >100 kU/L at ECRHS I, II and/or III

[d] having specific IgE >0.35 kU/L for at least one among house-dust mite, timothy grass, or cat allergens at ECRHS I, II and/or III

[e] this characteristic (or a closely related one) was considered for disease definition

Table E9

Review of cohort studies comparing FEV_1 decline between subjects with asthma+COPD and COPD alone.

				COPD alone		Asthma+COPD	
Reference	Setting (f-up time)	Source population	Participants' age and sex at the time of disease classification	Definition (number of subjects)	Adult-life change in FEV_1 [a]	Definition (number of subjects)	Adult-life change in FEV_1 [a]
Fu et al. (6)	John Hunter hospital in Newcastle, Australia (f-up ~4 y)	Hospital-based outpatients with obstructive airway diseases, no current smokers	Mean age 69 y, 58% women	Post-BD FEV_1/FVC <0.7 + post-BD FEV_1 <80% predicted + no increased airflow variability (neither AHR nor BDR) (n=36)	-24 mL/y (post-BD)	Post-BD FEV_1/FVC <0.7 + post-BD FEV_1 <80% predicted + respiratory symptoms + increased airflow variability (either AHR or BDR) (n=55)	-14 mL/y (post-BD)
de Marco et al. (7)	European Community Respiratory Health Survey, European countries (f-up ~9 y)	General population + sample enriched for respiratory symptoms	Mean age 34 y, 53% women	Pre-BD FEV_1/FVC <LLN at baseline and f-up + one among: chronic bronchitis, dyspnoea, ≥10 pack-y smoked, occupational inhalant exposures (n=166)	-37 mL/y (pre-BD)	COPD + report of asthma + one among: current respiratory symptoms/medication, AHR *or* COPD + current respiratory symptoms + AHR (n=218)	-26 mL/y (pre-BD)
Lange et al. (8)	Copenhagen City Heart study, Denmark (f-up ~18 y)	General population	Mean age 57 y, 43% women	Post-BD FEV_1/FVC <0.7 + ≥10 pack-y smoked + neither report of asthma nor BDR (n=303)	-46 mL/y (pre-BD)	Post-BD FEV_1/FVC <0.7 regardless of smoking history + report of asthma before age 40 y (early-onset, n=62) or after age 40 y (late-onset, n=188)	-31 mL/y (pre-BD, early-onset) -51 mL/y (pre-BD, late-onset)
Suzuki et al. (9)	Hokkaido COPD cohort study, Japan (f-up ~5 y)	Hospital-based outpatients with diagnosed COPD	Mean age 69 y, 6% women	Respiratory specialist diagnosis confirmed by post-BD FEV_1/FVC <0.7 + ≥10 pack-y smoked (n=135) + no diagnosed asthma	-34 mL/y (post-BD)	COPD + 2 among: BDR, atopy, blood eosinophilia (n=31) + no diagnosed asthma	-27 mL/y (post-BD)
Tkacova et al. (10)	Lung Health Study, USA and Canada (f-up ~3 y)	Clinical trial	Median age 49 y, 37% women	Post-BD FEV_1/FVC <0.7 + FEV_1 55–90% predicted + smoker ≥10 cigs/day (n=4453)	-55 mL/y (pre-BD)	COPD + AHR (n=1434)	-65 mL/y (pre-BD)

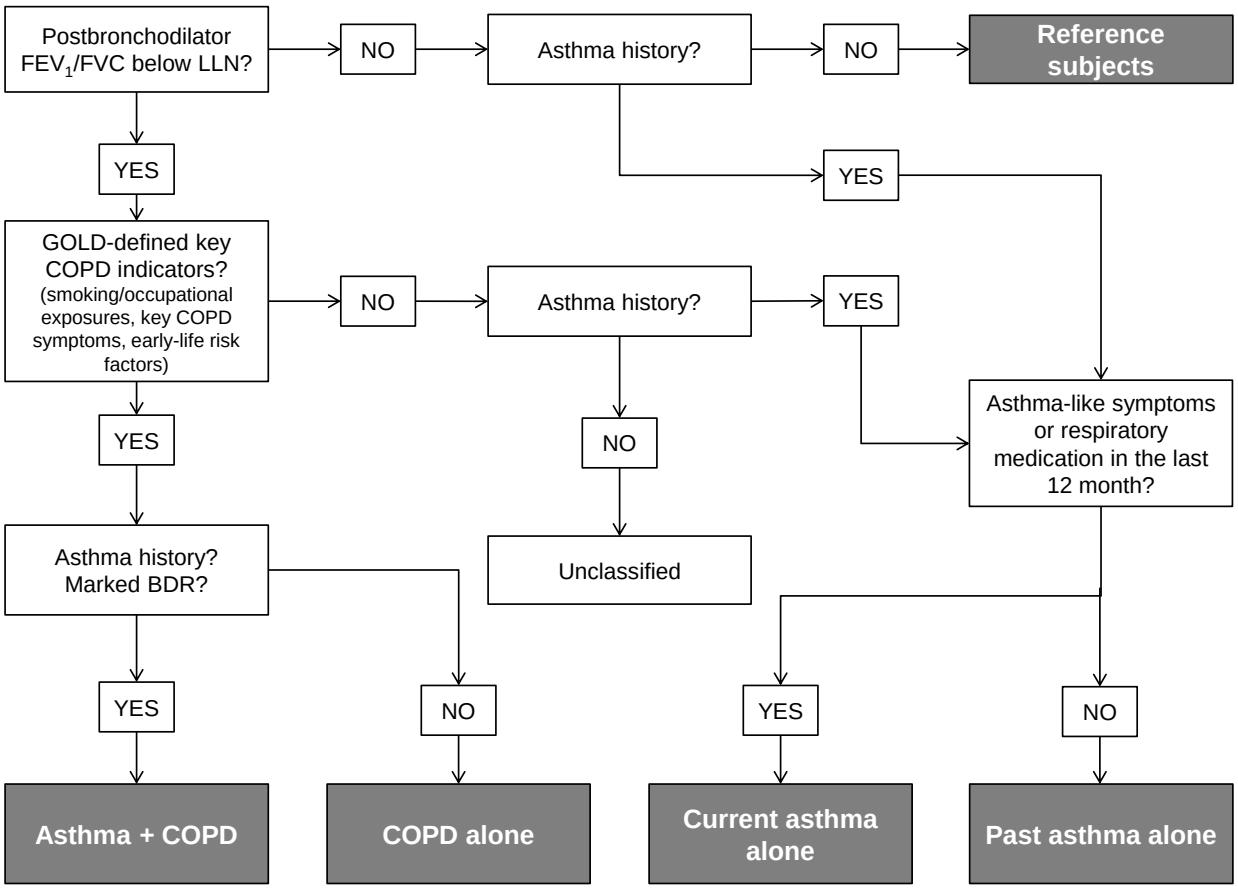
Bui et al. (11)	Tasmanian Longitudinal Health Study, Australia (f-up ~27 y)	General population + sample enriched for respiratory symptoms	Mean age 45 y, 49% women	Post-BD FEV_1/FVC <LLN, regardless of smoking (n=59)	-0.6% predicted/y (pre-BD)	COPD + history of asthma + current respiratory symptoms/ medication (n=68)	- 0.3% predicted/y (pre-BD)
Hayden et al. (12)	COPDGene study, United States (f-up ~5 y)	General population,	Mean age 68 y, 76% women	Post-BD FEV_1/FVC <0.7 + post-BD FEV_1 <80% predicted + ≥10 pack-y smoked (n=1,359)	-38 mL/y (post-BD)	COPD + report of asthma before age 40 y (n=242)	-32 mL/y (post-BD)
Park et al. (13)	Korean Obstructive Lung Disease cohort study, Republic of Korea (f-up ~6 y)	Hospital-based outpatients with COPD	Mean age 66 y, 2% women	Post-BD FEV_1/FVC <0.7 + ≥10 pack-y smoked (n=192)	-29 mL/y (pre-BD)	COPD + either history of asthma or marked BDR + one among: history of atopy/allergic rhinitis, BDR on two occasions, blood eosinophilia (n=47)	-14 mL/y (pre-BD)
Barrecheguren et al. (14)	Canadian Cohort Obstructive Lung Disease study, Canada (f-up ~3 y)	General population	Mean age 67 y, 39% women	Post-BD FEV_1/FVC <0.70 + history of smoking + none of these: BDR, atopy, report of physician-diagnosed asthma (n=182)	-51 mL/yr (pre-BD)	Post-BD FEV_1/FVC <0.70 + history of smoking + one among: BDR, atopy, report of physician-diagnosed asthma (n=188)	-44 mL/y (pre-BD)
Marcon et al. (present study	European Community Respiratory Health Survey, European countries (f-up ~20 y)	General population + sample enriched for respiratory symptoms	Mean age 54 y, 53% women	Post-BD FEV_1/FVC <LLN + one among: history of smoking, occupational exposures, key symptoms, early-life risk factors + no history of asthma + no marked BDR	-46.5 mL/yr (pre-BD)	Post-BD FEV_1/FVC <LLN + one among: history of smoking, occupational exposures, key symptoms, early-life risk factors + one among: history of asthma, marked BDR	-36.5 mL/yr (pre-BD)

AHR = airway hyperresponsiveness; BD= bronchodilator; BDR= bronchodilator responsiveness; f-up = follow-up; LLN = lower limit of normal

[a] Unadjusted estimates; if not provided in the original publications, estimates adjusted for basic covariates were reported; some data were extrapolated from illustrations

Figure E1

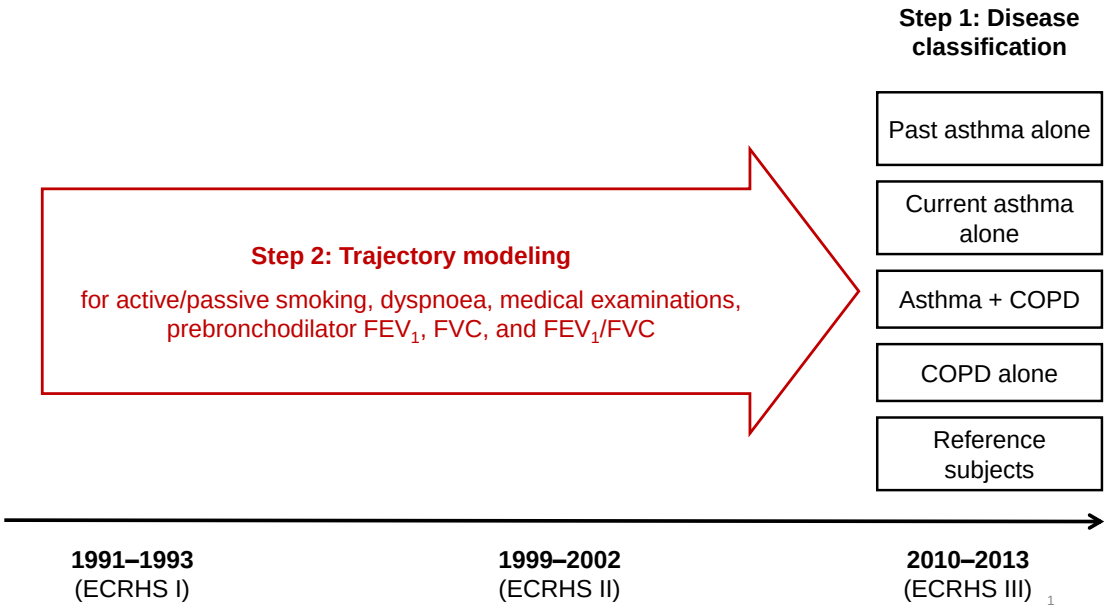
Decision tree illustrating disease classification at ECRHS III. [a]



[a] All the criteria composing disease definitions were fulfilled at the time of ECRHS III either on the basis of data measured at ECRHS III (postbronchodilator FEV_1/FVC, marked bronchodilator responsiveness [BDR], key COPD symptoms, asthma-like symptoms or respiratory medication in the last 12 months), or based on cumulative data (history of smoking/occupational exposures, history of asthma) or past data (early-life respiratory infections).

Figure E2

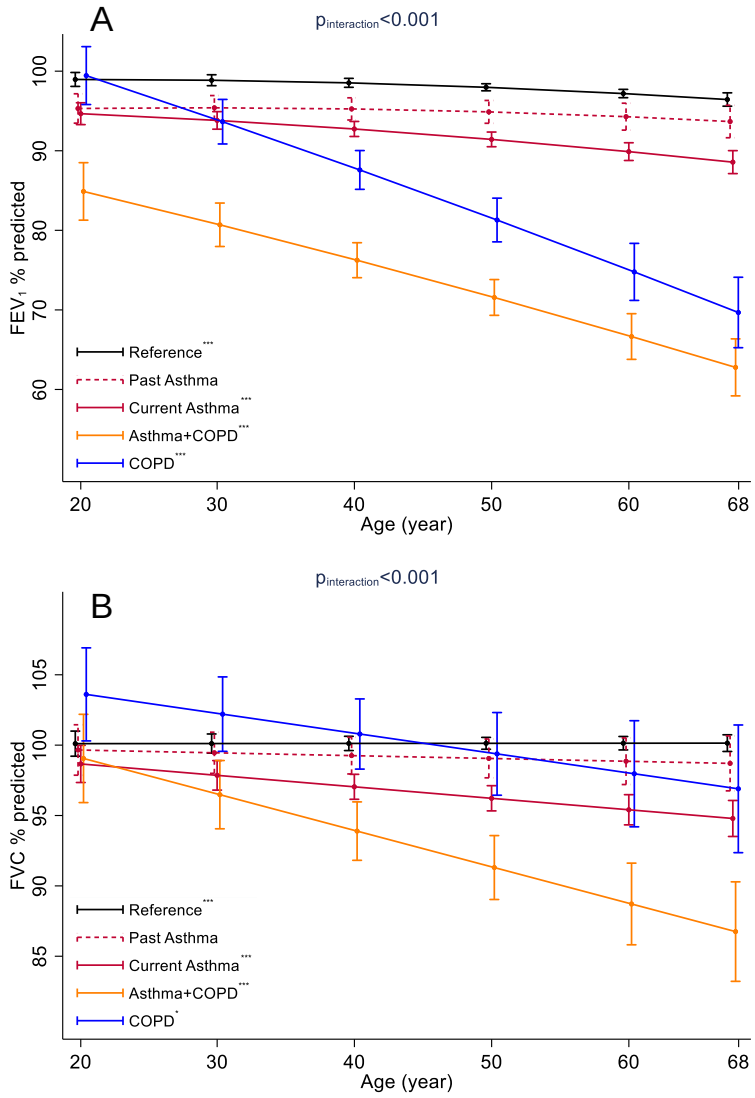
Study timeline. [a]



[a] Disease classification was conducted at ECRHS III, when postbronchodilator lung function data were available (step 1). Then, past trajectories of participants' characteristics were modelled for these phenotypes (step 2).

Figure E3

Predicted trajectories for mean prebronchodilator FEV_1 % predicted (A) and FVC % predicted (B) as a function of disease group and age. [a]

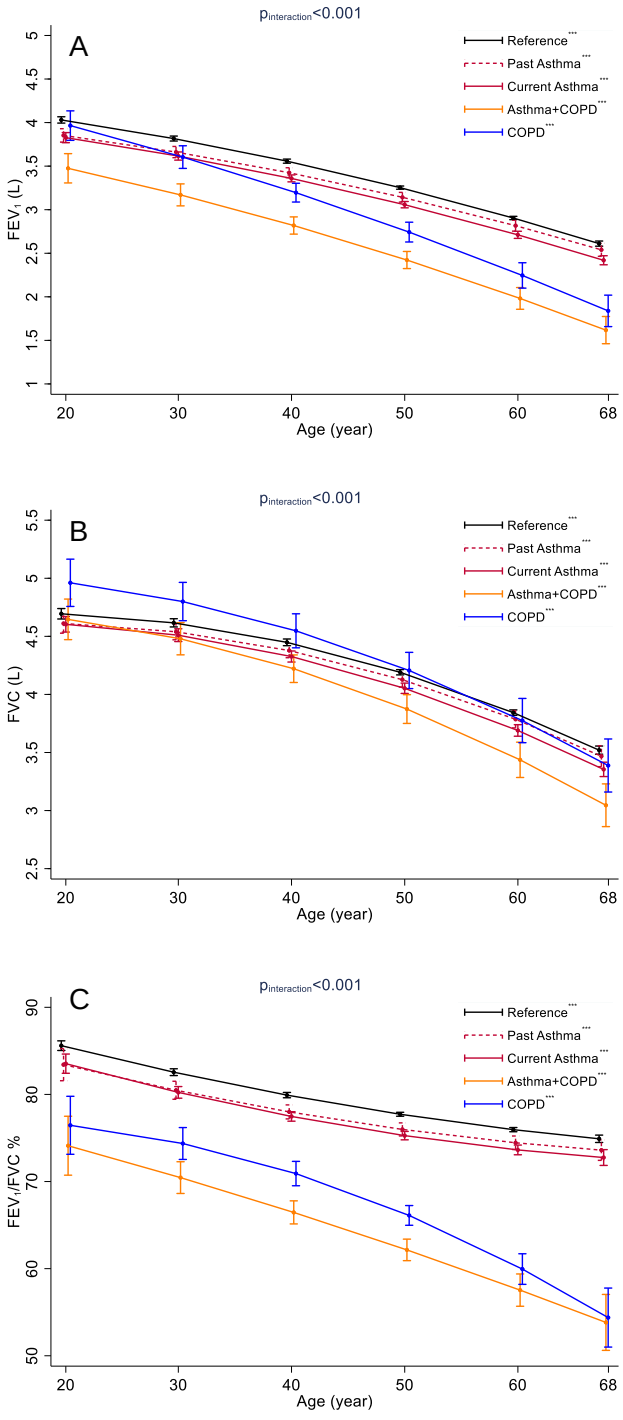


[a] N. of subjects contributing data = 4831 (FEV_1) and 4822 (FVC). $p_{interaction}$ obtained by Wald test (null hypothesis: true trajectories do not vary by disease group). The vertical lines represent 95% confidence intervals. Spirometer type was set to NDD EasyOne; quantitative/indicator independent variables were set equal to the mean/proportion calculated over the set of subjects included.

* p <0.05, *** 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)

Figure E4

Predicted trajectories for mean prebronchodilator FEV_1 (A), FVC (B), and FEV_1/FVC ratio (C) as a function of disease group and age. **Sensitivity analysis restricted to the subjects with three lung function measurements** (ECRHS I, II and III). [a]

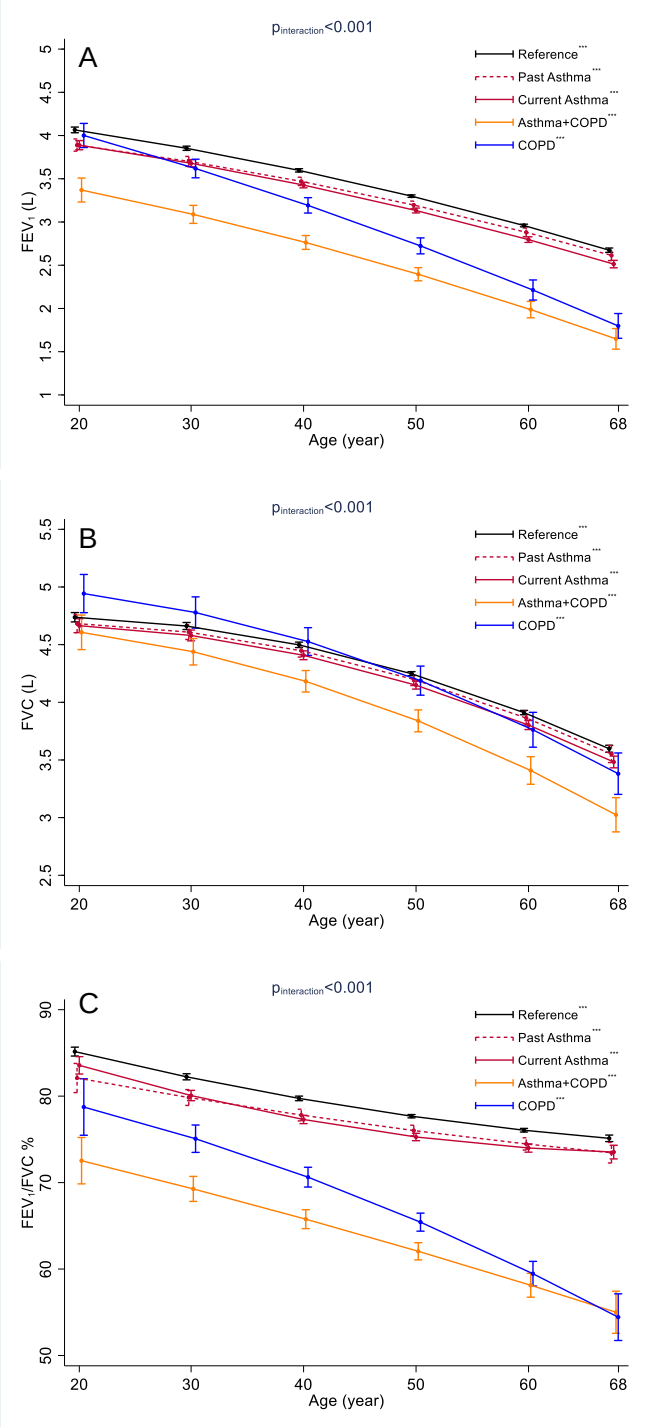


[a] N. of subjects contributing data = 3197 (FEV_1), 3197 (FVC), and 3196 (FEV_1/FVC). $p_{interaction}$ obtained by Wald test (null hypothesis: true trajectories do not vary by disease group). The vertical lines represent 95% confidence intervals. Spirometer type was set to NDD EasyOne; quantitative/indicator 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)

Figure E5

Predicted trajectories for mean prebronchodilator FEV_1 (A), FVC (B), and FEV_1/FVC ratio (C) as a function of disease group and age. **Sensitivity analysis excluding the subjects with PRISm** (postbronchodilator FEV_1/FVC >LLN in combination with FEV_1 or FVC <LLN). [a]

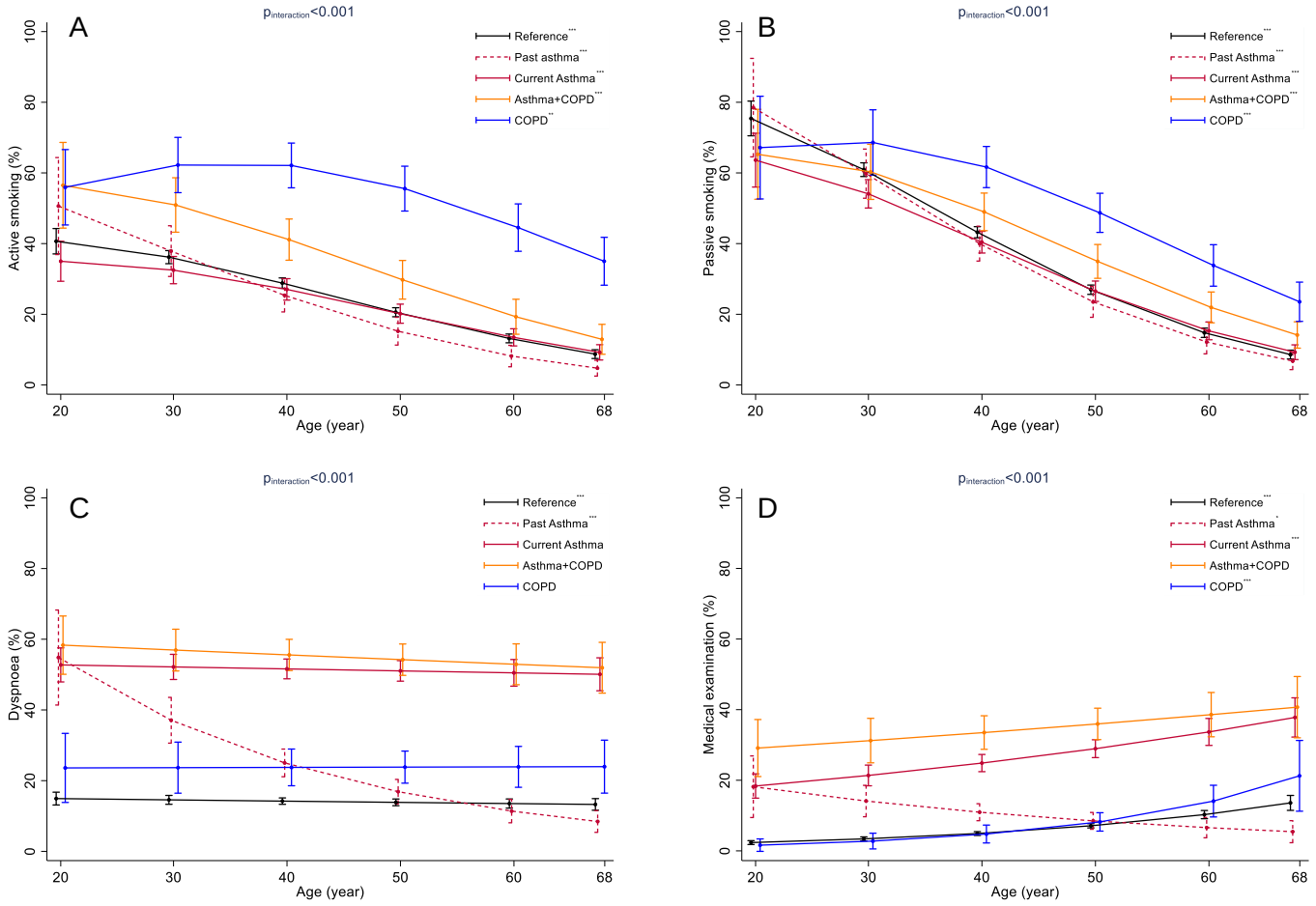


[a] N. of subjects contributing data = 4559 (FEV_1), 4552 (FVC), and 4547 (FEV_1/FVC). $p_{interaction}$ obtained by Wald test (null hypothesis: true trajectories do not vary by disease group). The vertical lines represent 95% confidence intervals. Spirometer type was set to NDD EasyOne; quantitative/indicator 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)

Figure E6

Predicted trajectories for the proportion of subjects reporting active smoking (A), passive smoking (B), dyspnoea (C), or having been seen by a physician during the last 12 months (D) as a function of disease group and age. **Sensitivity analysis using the GOLD fixed cut-off criterion for disease classification**. [a]

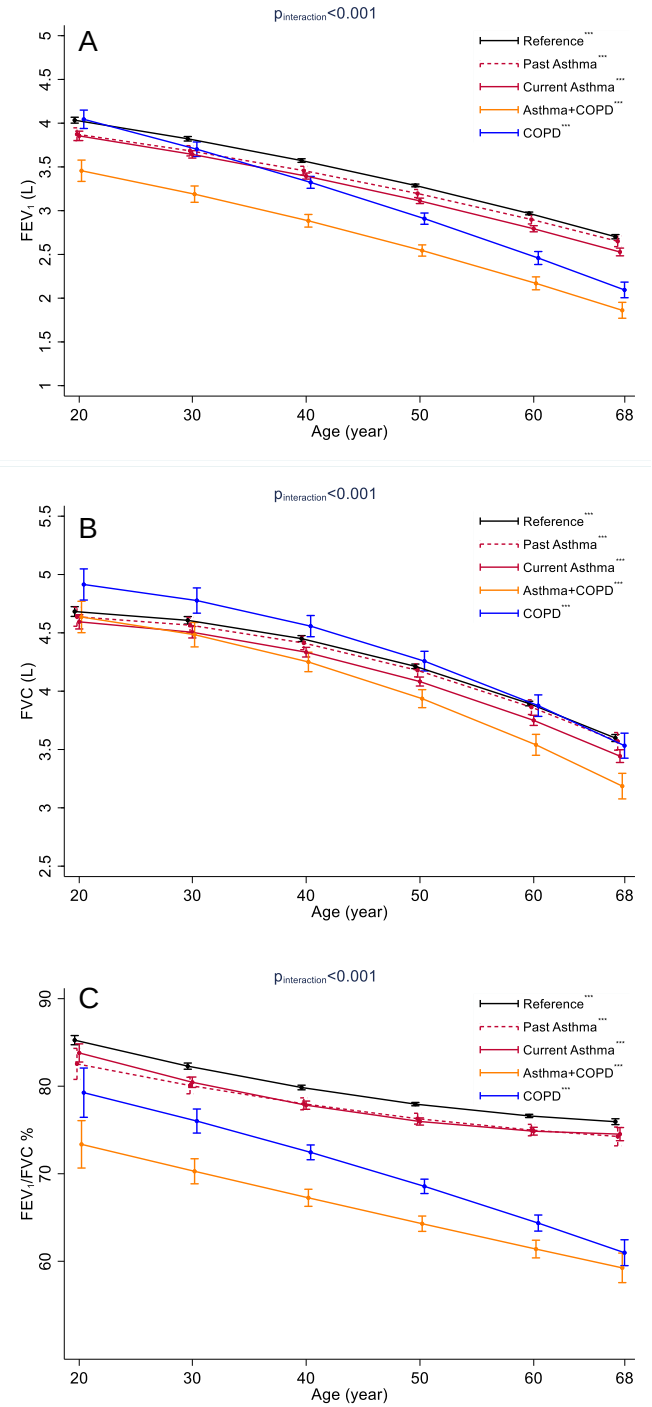


[a] N. of subjects contributing data = 4818. $p_{interaction}$ obtained by Wald test (null hypothesis: true trajectories do not vary by disease group). The vertical lines represent 95% confidence intervals. Quantitative/indicator independent variables were set equal to the mean/proportion calculated over the set of subjects included.

* p<0.05, ** p<0.01, *** p<0.001 for the test of significance of the age-related trend within a disease group (null hypothesis: true proportion is constant across ages)

Figure E7

Predicted trajectories for mean prebronchodilator FEV_1 (A), FVC (B), and FEV_1/FVC ratio (C) as a function of disease group and age. **Sensitivity analysis using the GOLD fixed cut-off criterion for disease classification.** [a]



[a] N. 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

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