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BMJ Open Respiratory Research

Phenotyping asthma with airflow obstruction in middle-aged and older adults: a CADSET clinical research collaboration

Xander Bertels (1,2), Ahmed Edris (1,2), Judith Garcia-Aymerich (1,3), America Rosa Faner, And Start, Howraman Meteran, Torben Sigsgaard, Peter Alter, Claus Vogelmeier, Nuria Olvera, Start, Nazanin Zounemat Kermani, Alvar Agusti, And Start, Gavin C Donaldson (1,1), Jadwiga A Wedzicha, America Guy G Brusselle, And Start, Helena Backman, Characteria Rommark, Anne Lindberg (1,1), Judith M Vonk, Anne Lindberg, International Advantage (1,2), Anne Lindberg, Anne Lindberg, Anne Lindberg, Anne Lindberg, Anne Lindberg, Anne Lindberg, International Advantage (1,2), Anne Lindberg, International Advantage (1,2), Anne Lindberg, Anne Lindberg

ABSTRACT

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For numbered affiliations see end of article.

Correspondence to

Professor Lies Lahousse; lies.lahousse@ugent.be **Background** The prevalence and clinical profile of asthma with airflow obstruction (A0) remain uncertain. We aimed to phenotype A0 in population- and clinic-based cohorts.

Methods This cross-sectional multicohort study included adults ≥50 years from nine CADSET cohorts with spirometry data (N=69789). AO was defined as ever diagnosed asthma with pre-BD or post-BD FEV₁/FVC <0.7 in population-based and clinic-based cohorts, respectively. Clinical characteristics and comorbidities of AO were compared with asthma without airflow obstruction (asthma-only) and chronic obstructive pulmonary disease (COPD) without asthma history (COPD-only). ORs for comorbidities adjusted for age, sex, smoking status and body mass index (BMI) were meta-analysed using a random effects model.

Results The prevalence of AO was 2.1% (95% CI 2.0% to 2.2%) in population-based, 21.1% (95% Cl 18.6% to 23.8%) in asthma-based and 16.9% (95% CI 15.8% to 17.9%) in COPD-based cohorts. AO patients had more often clinically relevant dyspnoea (modified Medical Research Council score ≥ 2) than asthma-only (+14.4 and +14.7 percentage points) and COPD-only (+24.0 and +5.0 percentage points) in population-based and clinic-based cohorts, respectively. AO patients had more often elevated blood eosinophil counts (>300 cells/ µL), although only significant in population-based cohorts. Compared with asthma-only, AO patients were more often men, current smokers, with a lower BMI, had less often obesity and had more often chronic bronchitis. Compared with COPD-only, AO patients were younger, less often current smokers and had less pack-years. In the general population, AO patients had a higher risk of coronary artery disease than asthma-only and COPD-only (OR=2.09 (95% CI 1.26 to 3.47) and OR=1.89 (95% CI 1.10 to 3.24), respectively) and of depression (OR=1.41 (95% CI 1.19 to 1.67)), osteoporosis (OR=2.30 (95% CI 1.43 to 3.72)) and gastro-oesophageal reflux disease (OR=1.68 (95% CI 1.06 to 2.68)) than COPD-only, independent of age, sex, smoking status and BMI.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Asthma with airflow obstruction (A0) is associated with higher exacerbation rates and mortality compared with asthma without airflow obstruction.

WHAT THIS STUDY ADDS

⇒ A0 patients show more clinically relevant dyspnoea compared with both asthma without airflow obstruction and COPD without asthma history. Second, A0 patients from the general population had more often elevated blood eosinophil counts and are at an increased risk of coronary artery disease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study may facilitate early detection of (mild) A0 and concomitant coronary artery disease in clinical practice.

Conclusions A0 is a relatively prevalent respiratory phenotype associated with more dyspnoea and a higher risk of coronary artery disease and elevated blood eosinophil counts in the general population compared with both asthma-only and COPD-only.

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are two prevalent chronic respiratory diseases with overlapping phenotypes and endotypes.^{1–3} Distinguishing between both diseases may, therefore, be difficult, yet essential as both diseases require different treatment decisions.^{4–6} Importantly, there is a recognised additional clinical phenotype called asthma with fixed airflow



obstruction (AFO), consisting of patients with asthma who develop irreversible airflow obstruction (ie, fixed obstruction) with a reduced response to β_2 -adrenergic agonists.³ This has been attributed to airway remodelling and persistent inflammation, which is potentially linked to steroid resistance, yet the mechanisms leading to fixed AO and associated comorbidities are not fully understood.⁷⁻⁹ Clinically, these patients show a worse prognosis and are expected to have more frequent and more severe exacerbations compared with patients with asthma with reversible airflow obstruction.⁷⁻⁹ Hence, early recognition of asthma with AO is important as it may affect the patient's prognosis.⁷

AO primarily affects severe asthma patients (40%-60% of severe asthmatics are estimated to have airway obstruction) and is more prevalent with older age.^{8 10-13} However, the prevalence and optimal treatment strategy of AO, including in AFO, have been a subject of debate.¹ The target population, seniority and specialisation of physicians undertaking the diagnosis of asthma, and definition of airflow obstruction (FEV₁/FVC <0.7 or below lower limit of normal (LLN)) all affect the prevalence of AO.^{7 14-16} Furthermore, randomised clinical trials in asthma traditionally excluded patients with a rich smoking history while COPD trials excluded patients with a history of asthma.^{17 18}

Altogether, the occurrence and clinical profile of AO patients remain unclear. Hence, our study aimed: (1) to determine the prevalence of AO in population-based and clinic-based cohorts, (2) to compare the clinical characteristics between AO patients and asthma without airflow obstruction (asthma-only) and COPD without asthma history (COPD-only) and (3) to compare the prevalence of comorbidities in patients with AO versus patients with asthma-only or COPD-only.

METHODS

Study design and population

This analysis was performed in the framework of CADSET,¹⁹ a European Respiratory Society Clinical Research Collaboration. Participants \geq 50 years with interpretable spirometry and information on asthma diagnosis were cross-sectionally analysed in nine cohort studies: two asthma-based (OLIN and U-BIOPRED), four COPD/ smoker-based (COSYCONET, ECLIPSE, PAC-COPD and Urban Training) and three population-based cohorts (LifeLines, Danish Twin Registry and Rotterdam Study). The design of all cohorts has been published in detail and summarised in online supplemental table S1.^{20–28}

Definitions

AO was defined as ever-diagnosed asthma with airflow limitation (a prebronchodilator FEV₁/FVC <0.7 in population-based studies and a postbronchodilator FEV₁/FVC <0.7 in clinic-based cohorts). Asthma-only was defined as ever physician-diagnosis of asthma and FEV₁/FVC \geq 0.7. COPD-only was defined as FEV₁/FVC<0.7

without asthma history. Asthma in COPD-based cohorts includes both current asthma, as this was not an exclusion criterium of the included COPD cohorts, and asthma in remission. Additionally, $FEV_1/FVC \ll LLN$ was used to define airflow obstruction. Data collection and definitions are reported in the online supplemental file.

Statistical analysis

The prevalence of AO was cross-sectionally meta-analysed by a common effect model using inverse-variance weighting. Clinical characteristics and comorbidities were meta-analysed by a random effects model and logistic regression was performed to adjust the prevalence of comorbidities for age, sex, smoking status and body mass index (BMI). On the cohort level, continuous variables were summarised as means (SD), except for C reactive protein and IgE levels (medians (IQR)). Mean differences (continuous variables) and risk differences (categorical variables) were tested in comparison to the AO group. All comparisons were stratified per cohort type, that is, separately for population-based, asthmabased and COPD-based cohorts. Statistical analysis was performed in R.V.4.1.1 (Vienna, Austria) using the 'meta' package.^{29 30}

RESULTS

Prevalence of asthma with A0

A total of 69789 participants were included in this study. The prevalence of AO (figure 1) was estimated to be 2.1% (95% CI 2.0% to 2.2%) in three population-based cohorts (n=63459), 21.1% (95% CI 18.6% to 23.8%) in two asthma-based cohorts (n=928) and 16.9% (95% CI 15.8% to 17.9%) in four COPD-based cohorts (n=5402). The prevalence of AO was highest in U-BIOPRED and ECLIPSE, both showing the lowest mean FEV₁% predicted and FEV₁/FVC values of their respective cohort types (online supplemental table S2).

When FEV₁/FVC <LLN was used to define AO (online supplemental figure S1), the estimated prevalence of AO was relatively lower in population-based (1.2% vs 2.1%) and asthma-based cohorts (16.4% vs 21.1%). In COPD-based cohorts, the prevalence remained, however, more similar (15.5% vs 16.9%).

Characteristics of patients with AO

Clinical characteristics of patients with AO are presented in table 1 and were compared with asthma-only and COPD-only in population-based and in more symptomatic clinic-based cohorts, reflected by more dyspnoea and chronic bronchitis. AO patients had significantly more often clinically relevant dyspnoea (modified Medical Research Council score \geq 2) than asthma-only (+14.4 and +14.7 percentage points) and COPD-only (+24.0 and +5.0 percentage points) in population-based and clinic-based cohorts, respectively.

	AO n	Total n	Proportion (%) [95%CI]	Weight (common)	Weight (random)	Inverse–variance method
1) Population-based cohorts	5					
Lifelines	931	48,406	1.9 [1.8; 2.0]	71.8%	33.4%	•
DTR	261	9,611	2.7 [2.4; 3.1]	20.0%	33.4%	Œ
Rotterdam Study	106	5,442	1.9 [1.6; 2.4]	8.2%	33.2%	₩
Common effect model		63,459	2.1 [2.0; 2.2]	100.0%		•
Random effects model			2.2 [1.7; 2.7]		100.0%	•
Heterogeneity: $I^2 = 92.1\%$, $t^2 = 0.04$,	$c_2^2 = 2$	5.16 (<i>p</i> <	0.001)			
2) Asthma-based cohorts						
OLIN	128	646	19.8 [16.8; 23.1]	66.8%	50.2%	
U–BIOPRED	67	282	23.8 [18.9; 29.2]	33.2%	49.8%	
Common effect model		928	21.1 [18.6; 23.8]	100.0%		•
Random effects model			21.4 [17.8; 25.4]		100.0%	
Heterogeneity: $I^2 = 45.5\%$, $t^2 = 0.01$,	$c_1^2 = 1$.84 (<i>p</i> = 0	0.18)			
3) COPD-based cohorts						
COSYCONET	371	2,599	14.3 [13.0; 15.7]	45.1%	25.5%	<u>⊕</u>
ECLIPSE	448	2,075	21.6 [19.8; 23.4]	49.8%	25.5%	
Urban Training	15	399	3.8 [2.1; 6.1]	2.0%	24.3%	
PAC-COPD	23	329	7.0 [4.5; 10.3]	3.0%	24.7%	e
Common effect model		5,402	16.9 [15.8; 17.9]	100.0%		•
Random effects model			10.0 [4.6; 20.4]		100.0%	
Heterogeneity: $I^2 = 97.2\%$, $t^2 = 0.70$,	$c_{3}^{2} = 1$	05.45 (p ·	< 0.001)			
						0 5 10 15 20 25 30
						Prevalence (%) of AO

Figure 1 Meta-analysed prevalence of asthma with airflow obstruction (AO) in adults aged 50 years and older in populationbased and clinic-based cohorts. COPD, chronic obstructive pulmonary disease. DTR, Danish Twin Registry.

Compared with asthma-only, AO patients were more frequently men, current smokers, had a lower $FEV_1\%$ predicted and BMI, had less often obesity and had more often chronic bronchitis. Moreover, AO patients had more often elevated blood eosinophil counts (>300 cells/ μ L), were less frequently never smokers and had more pack-years in population-based cohorts, whereas they had a lower FVC% predicted and higher white blood cell counts in clinic-based cohorts.

Compared with COPD-only, AO patients were significantly younger, less frequently current smokers and had less pack-years. Specifically in population-based cohorts, patients with AO also showed a higher BMI, a lower FEV₁% and FVC% predicted, were more frequently never smokers, obese and had more frequently allergic disease history, chronic bronchitis and elevated blood eosinophil counts.

The number of exacerbations in the year prior to spirometry was evaluated in clinic-based cohorts. AO patients showed a higher prevalence of individuals with at least two exacerbations in prior year compared with COPD-only patients (54.0% vs 45.7%, p<0.01) in ECLIPSE. This association remained significant after adjusting for age, sex, smoking status and BMI (OR=1.76 (95% CI 1.44 to 2.15), p<0.01). Furthermore, AO patients showed a modestly higher number of severe exacerbations (β =0.09 (95% CI 0.01 to 0.17), p=0.04) compared with COPD-only in COSYCONET, corrected for age, sex,

smoking status and BMI. Compared with asthma-only, AO patients showed a borderline significantly higher risk of having at least one exacerbation in prior year (OR=2.1 (95% CI 1.0 to 4.2), p=0.05) in U-BIOPRED.

Overall, similar differences in characteristics were observed for LLN-defined AO (online supplemental table S4-S6), while age and sex differences were less pronounced. Compared with asthma-only, LLN-defined AO additionally showed a lower FVC% and more allergic disease history in population-based cohorts and more often elevated blood eosinophil counts in clinic-based cohorts. In contrast, the increased exacerbation risk of AO compared with asthma-only in U-BIOPRED was no longer significant using LLN-defined AO (OR=1.6 (95% CI 0.75 to 3.42), p=0.23).

Comorbidities of AO

The prevalence of AO comorbidities, adjusted for age, sex, smoking status and BMI, was compared with asthmaonly and COPD-only (figure 2). Overall, patients with AO had a significantly higher risk of coronary artery disease (CAD) compared with both asthma-only (OR=2.09 (95% CI 1.26 to 3.47), p<0.01) and COPD-only (OR=1.89 (95% CI 1.10 to 3.24), p=0.02) in population-based cohorts. In clinic-based cohorts, a similar trend was observed compared with asthma-only but not when compared with COPD-only.

Table 1 Meta-analysed characteristics	of AO compared wit	h asthma-only and	COPD-only in pop	ulation-based and	clinic-based coho	orts	
	Population-based	cohorts		Asthma-based cc	horts	COPD-based coh	orts
	AO	Asthma-only	COPD-only	AO	Asthma-only	AO	COPD-only
Characteristics							
Age (years), mean (95% CI)	63.8 (59.4–68.3)	62.5 (55.8–69.2)	65.6 (60.1–71.0)	61.7 (60.7–62.7)	58.7 (55.9–61.5)	65.6 (63.3–67.9)	67.0 (64.7–69.4)
Female, prop (95% CI)	53.3 (50.5–56.0)	64.4 (59.1–69.7)	46.9 (42.9–51.0)	42.3 (34.1–50.6)	60.6 (57.1–64.1)	30.7 (6.1–55.3)	22.3 (8.5–36.1)
BMI (kg/m ²), mean (95% Cl)	26.7 (26.4–26.9)	28.5 (27.8–29.2)	26.2 (26.1–26.4)	26.4 (24.5–28.4)	28.3 (26.0–30.6)	27.7 (26.1–29.3)	27.3 (26.4–28.2)
Underweight, prop (95% CI)	1.0 (0.5–1.5)	0.2 (0.0–0.5)	0.9 (0.2–1.6)	1.6 (0.0–3.4)	0.8 (0.0–2.6)	3.7 (1.7–5.7)	2.6 (1.0–4.3)
Normal weight, prop (95% Cl)	36.4 (32.3–40.4)	23.4 (19.5–27.2)	38.7 (35.7–41.6)	40.4 (23.3–57.4)	28.3 (21.9–34.7)	28.4 (14.2–42.5)	30.3 (22.6–37.9)
Overweight, prop (95% CI)	42.9 (36.9–48.9)	42.1 (39.2–45.1)	45.0 (40.8–49.2)	41.4 (34.3–48.5)	40.1 (29.5–50.7)	36.9 (33.6–40.1)	38.2 (35.3–41.0)
Obese, prop (95% CI)	18.5 (16.4–20.6)	35.0 (27.6–42.3)	15.4 (13.7–17.1)	16.3 (0.0–32.8)	31.1 (12.3–50.0)	23.2 (20.1–26.3)	27.9 (21.4–34.3)
Never smoker, prop (95% Cl)	29.7 (24.4–35.0)	37.9 (34.4–41.5)	22.3 (17.4–27.1)	10.2 (5.2–15.1)	26.2 (0.0–61.1)	6.4 (0.0–15.2)	1.7 (0.0–3.9)
Former smoker, prop (95% CI)	52.8 (50.0–55.5)	52.8 (46.7–59.0)	49.2 (39.5–59.0)	43.7 (17.0–70.3)	34.2 (30.8–37.7)	66.5 (63.3–69.6)	61.2 (44.0–78.4)
Current smoker, prop (95% CI)	17.4 (9.2–25.5)	9.3 (6.4–12.1)	28.4 (19.7–37.2)	46.3 (14.7–77.9)	39.7 (3.7–75.7)	21.3 (5.1–37.5)	37.1 (18.6–55.5)
Pack-years, mean (95% CI)	21.2 (16.5–25.9)	15.4 (11.2–19.5)	25.3 (21.6–29.0)	18.2 (11.4–25.0)	17.5 (13.5–21.5)	44.1 (34.5–53.8)	57.2 (47.2–67.2)
mMRC score≥2, prop (95% Cl)	38.8 (21.9–55.7)	24.4 (5.6–43.2)	14.8 (0.4–29.2)	54.7 (46.1–63.3)	40.0 (35.7–44.2)	51.3 (31.4–71.2)	46.3 (32.4–60.2)
Allergic disease history, prop (95% Cl)	75.7 (73.0–78.5)	74.9 (72.4–77.4)	42.9 (41.7–44.0)	70.3 (47.3–93.3)	73.2 (61.9–84.4)	44.1 (21.2–66.9)	29.9 (24.0–35.8)
Chronic bronchitis, prop (95% Cl)	20.3 (10.9–29.8)	14.4 (9.7–19.2)	10.4 (5.6–15.2)	31.7 (1.8–61.5)	23.3 (0.0–46.9)	57.2 (31.1–83.2)	53.3 (34.9–71.7)
Emphysema, prop (95% Cl)	I	I	I	I	I	47.8 (4.4–91.1)	46.5 (4.5–88.6)
Spirometry							
FEV ₁ (%) predicted, mean (95% CI)	75.0 (69.7–80.3)	95.1 (92.5–97.8)	81.8 (76.0–87.7)	54.9 (41.1–68.6)	80.4 (66.5–94.4)	51.7 (45.2–58.1)	51.1 (46.5–55.7)
FVC (%) predicted, mean (95% CI)	93.0 (85.5–100.5)	95.9 (92.1–99.7)	97.8 (90.4–105.1)	78.9 (76.2–81.6)	88.8 (82.8–94.7)	77.2 (72.9–81.5)	77.1 (74.3–79.9)
FEV ₁ /FVC (%), mean (95% Cl)	61.6 (59.7–63.6)	77.0 (76.4–77.6)	63.9 (63.4–64.5)	54.2 (41.2–67.2)	72.8 (57.7–87.8)	51.6 (46.3–56.9)	50.2 (46.3–54.1)
Biomarkers							
Peripheral blood WBC (10 ⁹ cells/L), mean (95% CI)	6.7 (5.7–7.8)	6.6 (5.5–7.7)	6.9 (5.4–8.4)	8.8 (7.8–9.7)	7.6 (7.2–8.0)	7.9 (7.7–8.1)	7.7 (7.2–8.2)
BEC above 300 cells/µL, prop (95% Cl)	28.3 (25.3–31.2)	18.0 (15.7–20.2)	15.7 (14.8–16.5)	47.0 (34.9–59.0)	35.9 (29.4–42.4)	24.0 (20.1–27.9)	18.6 (11.1–26.0)
Serum CRP (mg/dL), median (IQR)*	I	I	I	2.2 (3.5)	2.1 (3.8)	3.0 (3.8)	3.7 (5.0)
Serum IgE (ie,/mL), median (IQR)*	1	1	1	120 (292)	110 (221)	78 (192)	54 (116)
*Summary statistics of individual cohorts were n AO, asthma with airflow obstruction; BEC, blooc of FEV1 to FVC; FVC, forced vital capacity; IgE,	neta-analysed, except fo d eosinophil counts; COI immunoglobulin E; mMF	or CRP and IgE for wh PD, chronic obstructiv RC, modified Medical	ich only single-study d e pulmonary disease; (Research Council Dysp	ata were available. CRP, C reactive protei noea; WBC, white blo	ı; FEV1, forced expira ood cell count.	atory volume in 1 seco	ond; FEV1/FVC, ratio



odds ratio

Figure 2 Meta-analysis of comorbidities among patients with asthma with airflow obstruction (AO) compared with COPD without a history of asthma (COPD-only) (A) and compared with asthma without airflow obstruction (asthma-only) (B). ORs were adjusted for age, sex, smoking status and body mass index. The order of comorbidities was based on the effect size compared with COPD-only in population-based cohorts. A detailed meta-analysis for each comorbidity, including individual study effects and statistics, is presented in the supplemental file (online supplemental figures S1.1-S1.9). Osteoporosis and GERD could not be meta-analysed in population-based cohorts and were calculated using data from the Danish Twin Registry (single-cohort data, (online supplemental table S7). Comorbidities in asthma-based cohorts could not be meta-analysed and were calculated using available data from U-BIOPRED (single-cohort data, (online supplemental table S7)). COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease.

Additionally, compared with COPD-only, patients with AO showed a higher risk of osteoporosis (OR=2.30 (95% CI 1.43 to 3.72), p<0.01), depression (OR=1.41 (95% CI 1.19 to 1.67), p<0.01) and gastroesophageal reflux disease (GERD) (OR=1.68 (95% CI 1.06 to 2.68), p=0.03) in population-based cohorts. A similar trend was

observed for GERD in clinic-based studies. In contrast, the effect size for osteoporosis and depression showed no trend in clinic-based studies, which was due to an opposite direction-of-effect in COSYCONET compared to ECLIPSE (online supplemental figures S2.1 and S2.2, respectively).

Detailed meta-analyses of the OR (online supplemental figures S2.1-S2.9, online supplemental table S7) and crude prevalence (online supplemental figures S3.1-S3.9, online supplemental table S9) of each comorbidity are reported in the online supplemental file, including individual cohort effects. LLN-defined AO showed similar trends for CAD, osteoporosis, depression and GERD in population-based studies, although less pronounced (online supplemental figure S4).

DISCUSSION

In this large multicohort study (N=69789), we have determined the prevalence of asthma with AO in the general population of adults \geq 50 years and in a more symptomatic clinic-based setting. AO affects up to 2% of middle-aged and older adults from the general population, about one in five older patients in asthma cohorts and 4% to 22%of patients in COPD-based cohorts. Our study showed that, irrespective of cohort type, AO patients suffered more often from dyspnoea compared with both asthma subjects without airflow obstruction (asthma-only) and COPD subjects without a history of asthma (COPD-only). Second, AO patients from the general population had higher blood eosinophil levels, a higher risk of CAD compared with asthma-only and COPD-only, and of osteoporosis, depression and GERD compared with COPDonly.

First, our estimated prevalence of AO in the general population and in asthma-based cohorts is in line with previous systematic and narrative reviews on so-called asthma-COPD overlap.^{2 31} Our findings also confirm that a considerable, but variable, percentage of patients with COPD (~17%, ranging from 4% to 22%) in clinic-based studies had a physician diagnosis of asthma. This high variability may be driven by differences in AO and the fact that asthma is an independent risk factor for COPD over time.³² The highest prevalence of AO was found in ECLIPSE, which also showed the highest severity of AO, while the two smallest studies (PAC-COPD and Urban Training) with the lowest AO prevalence comprised of fewer patients with severe AO. Our estimated prevalence is, however, lower than a previous review $(\sim 25\%)^{31}$ and estimates of asthma features in patients with COPD (eg, atopy) ranging up to 50%.³³ This may be attributed to the relatively older age of this study population and the potential of underdiagnosis of asthma in the elderly.^{34 35}

Second, defining AO based on the LLN resulted in a lower prevalence of AO in the general population, in line with previous literature.³⁶ Hence, older adults with mild airflow limitation were likely included in the AO and COPD-only groups of the general population. In contrast, both definitions led to a similar prevalence in ECLIPSE, a COPD-cohort, which includes patients with more severe AO. Further studies are needed to identify which patients with mild or borderline AO deteriorate to LLN-defined AO, as they may require additional treatment approaches.

Third, clinically relevant dyspnoea was more common in AO patients than in either asthma-only or COPDonly. This despite AO patients having similar spirometric values than COPD-only in clinic-based cohorts. This suggests that AO patients may have a higher symptomatologic burden for the same spirometric values compared with COPD in a clinic-based setting. Hence, the development of dyspnoea in patients with AO may not be solely explained by AO only and should also be evaluated with other lung function tests (eg, residual lung volume).³⁷ AO patients also showed lower FVC% values compared with COPD-only in the general population and compared with asthma-only in a clinic-based setting. Future studies should investigate whether dyspnoea and low FVC in AO are determined by a concurrent increase in residual volume (eg, due to air trapping as a result of mucus plug $ging^{38}$ and/or small airway collapse³⁹) and investigate its relationship with lung function trajectories (eg, a lower maximally attained vital capacity at young adulthood and accelerated FEV, and/or FVC decline).⁴

In addition to the differences in dyspnoea and FVC, AO patients from the general population had more frequently chronic bronchitis and showed more often elevated blood eosinophil levels, in line with a previous study on AO in a population of mild asthmatics.⁴¹ It cannot be ruled out, however, that AO patients may predominantly show mixed inflammation, as markers of neutrophilic inflammation were not collected in our study. Furthermore, AO patients showed to be more often current smokers than asthma-only patients, emphasising that smoking is a risk factor for AO in asthmatics.⁴² Yet still, a third of AO patients were never smokers among the general population as well as in asthma cohorts. The percentage of never smokers among AO patients in clinical COPD cohorts was smaller due to the enrichment of patients with smoking history among these cohorts. Although the causes of obstructive airway disease in never smokers remain unclear, previous studies suggest that other environmental exposures (eg, biomass combustion) are important risk factors, especially in obese women.⁴³ Strikingly, AO patients had a similar prevalence of emphysema compared with clinic-based COPD, despite AO patients having a lower cumulative exposure to smoking. This indicates that emphysema is another potential pathogenic determinant of (fixed) AO in asthma patients next to airway remodelling.⁴⁴ Our study also contributes further evidence that AO patients in clinic-based studies are more likely to be exacerbators. AO patients had a higher risk for having at least two exacerbations and more severe exacerbations in last year compared with COPD-only, and a borderline higher risk for having at least one exacerbation in last year compared with asthma-only. This is in line with a previous post hoc analysis of the ATLANTIS study, showing that AO patients had more exacerbations during 1 year of follow-up.⁴¹ Given the potential of unadjusted confounders such as medication use, this association should, however, be interpreted cautiously. Further longitudinal cohort studies with deep phenotyping and strict definitions of environmental exposure may help disentangle the complex time-dependent interactions leading to (fixed) AO.

Fourth, our data demonstrate that the comorbidity burden in AO from the general population is considerably higher than in asthma-only or COPD-only. AO patients in population-based studies were at a higher risk for coronary artery disease (CAD) compared with asthma- and COPD-only, independent of age, sex, smoking status, and BMI. The pathophysiological link between obstructive lung function and CAD has been previously described and likely relates to systemic (eosinophilic) inflammation.⁴⁵ ⁴⁶ Furthermore, the higher prevalence of dyspnoea in AO patients may have led to physical inactivity and deconditioning,⁴⁷ which is an independent risk factor for CAD.⁴⁸ These results are in line with a previous study showing that patients with lateonset asthma and prebronchodilator FEV,<50% are at the highest risk for CAD among patients with obstructive airway diseases from the general population.⁴⁹ In clinicbased cohorts, AO patients showed a trend for increased CAD compared with asthma-only but not compared with COPD-only. This may be partly attributed to selection bias, where those with milder AO in the general population may show increased cardiovascular mortality making them less likely to be included in clinic-based cohorts, which primarily consisted of patients with more severe respiratory disease. In addition, the relative difference in FEV, may partly explain these findings. A previous mendelian randomisation study provided evidence for an inverse relationship between FEV, and CAD.⁵⁰ FEV, %was markedly lower in AO compared with COPD-only in population-based studies, but not significantly different compared with COPD-only in a clinical setting.

Finally, AO patients showed a higher risk for depression, osteoporosis and GERD compared with COPD-only in the general population. The increase in depression may be related to the higher dyspnoea burden in AO. Previous studies showed a cross-sectional link between dyspnoea and depression⁵¹, as well as a causal link with the development of symptoms of depression.⁵² Furthermore, previous evidence revealed overlapping genetics for major depressive disorder and asthma related to immunoglobulin gene hypermutation and DNA damage response.⁵³ In a clinic setting, AO patients showed a higher risk for osteoporosis and depression compared with COPD-only in COSYCONET, but an opposite direction of effect in ECLIPSE. These latter results, thus, require further investigation and replication in other clinic-based AO populations. Altogether, these results show the possible importance of dyspnoea and eosinophilic inflammation as potential contributors to the multimorbidity burden in asthma with AO, which may involve cardiovascular disease (coronary artery disease), metabolic disease (osteoporosis), gastrointestinal disease (GERD) and psychological disorders (depression).

Strengths of our study include that we assessed a wide array of patients in nine population-based and clinic-based

cohorts, spanning a multitude of global (mainly European) test sites. We compared clinically relevant characteristics between AO and asthma-only and COPD-only, aiming to single out this important understudied subtype of patients. However, our study also had limitations. We defined AO based on an ever physician-diagnosis of asthma, which could be subjected to recall and misclassification bias. Between-study differences in the diagnosis of asthma may have affected the results. Second, no postbronchodilator spirometry was performed in populationbased cohorts, resulting in possible inclusion of asthma patients with reversible airflow obstruction. The use of (long-acting) bronchodilators as part of standard-ofcare in general patients with diagnosed asthma may have minimised this; however, it cannot be completely excluded. Given that bronchodilator reversibility in the general population is as least as common in COPD as in asthma, possible inclusion of reversible flow limitation is expected in both groups when comparing AO to COPDonly among the population-based cohorts.⁵⁴ Third, results from the clinic-based cohorts may not be representative for all clinically diagnosed COPD or patients with asthma as these were mainly recruited from secondary or tertiary care centres. Fourth, each cohort may have had limitations in their data collection methods and some variables were not available in all cohorts. Finally, differences in the cohort populations may have resulted in heterogeneity between patients included in our study. To address this issue, we stratified our analysis on cohort type and used a random effects model. Future longitudinal studies should assess whether the findings presented in this study are more pronounced or limited to AO patients with current asthma and/or chronic persistent AO. Additionally, residual lung volume data may further elucidate the dyspnoea burden and possible FVC reduction in AO patients.

Author affiliations

¹Department of Bioanalysis, Ghent University, Gent, Belgium

²Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands ³Non-Communicable Diseases and Environment Programme, ISGlobal, Barcelona, Spain

⁴Centro Investigaciones Biomédicas en Red (CIBERES), Instituto de Salud Carlos III, Madrid, Spain

⁵Institut d'Investigacions Biomédiques August Pi i Sunyer (IDIBAPS), Hospital Clinic de Barcelona, Barcelona, Spain

⁶Department of Biomedical Sciences, University of Barcelona, Barcelona, Spain

⁷Department of Respiratory Medicine, Copenhagen University Hospital-Amager and Hvidovre, Kobenhagen, Denmark

⁸Environment, Occupation and Health, Danish Ramazzini Centre, Department of Public Health, Aarhus University, Aarhus, Denmark

⁹Department of Medicine, Pulmonary and Critical Care Medicine, Philipps University of Marburg, Marburg, Germany

¹⁰Department of Respiratory and Critical Care Medicine and Ludwig Boltzmann Institute for COPD and Respiratory Epidemiology, Otto Wagner Hospital, Vienna, Austria

¹¹National Heart and Lung Institute & Data Science Institute, Imperial College London, London, UK

¹²Department of Medicine, University of Barcelona, Barcelona, Spain
¹³Respiratory Institute, Hospital Clinic de Barcelona, Barcelona, Spain

¹⁴Department of Respiratory Medicine, Erasmus MC, Rotterdam, The Netherlands

¹⁵Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium

¹⁶Department of Public Health and Clinical Medicine, Umeå University, Umea, Sweden

¹⁷Department of Epidemiology, University Medical Centre Groningen, Groningen, The Netherlands

¹⁸Groningen Research Institute for Asthma and COPD (GRIAC), University Medical Centre Groningen, Groningen, The Netherlands

¹⁹Department of Pulmonology, University Medical Centre Groningen, Groningen, The Netherlands

Collaborators CADSET ERS Clinical Research Collaboration.

Contributors XB had full access to all summary statistics provided by the individual cohorts and takes responsibility for the integrity of the data and the accuracy of the data analysis as the guarantor. XB, JG-A, RF, HM, PA, NO, NZ and HB performed cohort-specific analyses. XB performed the formal analysis and meta-analysis of summary statistics, and XB and AE drafted the manuscript with guidance from LL. JG-A, RF, HM, TS, PA, CV, NO, NZK, AA, GCD, JAW, GGB, HB, ER, AL, JMV, KFC, IA, MvdB and LL contributed to manuscript revision. All authors have read and approved the final manuscript.

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ORCID iDs

Xander Bertels http://orcid.org/0000-0002-4815-9067 Ahmed Edris http://orcid.org/0000-0002-4049-5402 Judith Garcia-Aymerich http://orcid.org/0000-0002-7097-4586 Gavin C Donaldson http://orcid.org/0000-0002-5538-4190 Anne Lindberg http://orcid.org/0000-0002-3292-7471 Ian M Adcock http://orcid.org/0000-0003-2101-8843 Lies Lahousse http://orcid.org/0000-0002-3494-4363

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SUPPLEMENTAL MATERIAL

Phenotyping asthma with airflow obstruction in middle-aged and older adults: a CADSET Clinical Research Collaboration

Xander Bertels, MSc^{1,2}; Ahmed Edris, PhD^{1,2}; Judith Garcia-Aymerich, MD^{3,4,6}; Rosa Faner, PhD^{5,6}; Howraman Meteran, MD^{7,8}; Torben Sigsgaard, MD⁸; Peter Alter, MD⁹; Claus F Vogelmeier, MD^{9,10}; Nuria Olvera, MSc⁶; Nazanin Zounemat-Kermani, PhD¹¹; Alvar Agusti, MD^{5,6}; Gavin C. Donaldson, PhD¹¹; Jadwiga A. Wedzicha, MD¹¹; Guy G. Brusselle, MD^{2,13,14}; Helena Backman, PhD¹⁵; Eva Rönmark, PhD¹⁶; Anne Lindberg, MD¹⁶; Judith M. Vonk, PhD^{12,18}; Kian Fan Chung, MD¹¹; Ian M. Adcock, PhD¹¹; Maarten van den Berge, MD^{17,18}; Lies Lahousse, PhD^{1,2}, on behalf of the CADSET European Respiratory Society Clinical Research Collaboration

¹Department of Bioanalysis, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium; ²Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands; ³ISGlobal, Barcelona, Spain; ⁴Universitat Pompeu Fabra (UPF), Barcelona, Spain; ⁵Respiratory Institute, Hospital Clinic, IDIBAPS, University of Barcelona, Barcelona, Spain; 6CIBER Enfermedades Respiratorias, Hospital Clinic, Barcelona, Spain; 7Department of Respiratory Medicine, Copenhagen University Hospital-Amager and Hvidovre; 8Environment, Occupation and Health, Danish Ramazzini Centre, Department of Public Health, Aarhus University, Aarhus, Denmark; ⁹Department of Medicine, Pulmonary and Critical Care Medicine, Philipps University of Marburg; ¹⁰Department of Respiratory and Critical Care Medicine and Ludwig Boltzmann Institute for COPD and Respiratory Epidemiology, Otto Wagner Hospital, Vienna, Austria; ¹¹National Heart and Lung Institute & Data Science Institute, Imperial College London, London, UK; 12Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; ¹³Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium; ¹⁴Department of Respiratory Medicine, Erasmus MC, Rotterdam, The Netherlands; ¹⁵Department of Public Health and Clinical Medicine, Umeå University, Sweden; ¹⁶Department of Public Health and Clinical Medicine, Umeå University, Sweden; ¹⁷Department of Pulmonology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; ¹⁸Groningen Research Institute for Asthma and COPD (GRIAC), University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

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Table S1. Inclusion and exclusion criteria and ethics committee of cohorts.

Study:	COSYCONET
Type of study:	COPD-based cohort
Number of sites:	31 study centers in Germany
Population:	2,741 COPD patients
Inclusion Criteria:	- Aged 40 years and older,
	 Diagnosis of COPD (according to GOLD criteria) or chronic bronchitis,
	 Availability for repeated study visits over at least 18 months.
Exclusion Criteria:	- Having undergone major lung surgery (e.g., lung volume reduction, lung transplant),
	- Moderate or severe exacerbation within the last 4 weeks,
	- Having a lung tumor,
	- Physical or cognitive impairment resulting in an inability to walk or to understand the
E 11	intention of the project.
Ethics committees	The study protocol was approved by the central ethical committee in Marburg
	(Ethikkommission FB Medizin Marburg) and the respective local ethical committees: Bad
	(Ethikkommission Ärztokommor Borlin); Bochum (Ethikkommission Modizinischo
	Equilitat der BUB): Borstel (Ethikkommission Universität Lübeck): Coswig
	(Ethikkommission TII Dresden): Donaustauf (Ethikkommission Universitätsklinikum
	Regensburg): Essen (Ethikkommission Medizinische Eakultät Duisburg-Essen): Gießen
	(Ethikkommission Fachbereich Medizin): Greifswald (Ethikkommission
	Universitätsmedizin Greifswald); Großhansdorf (Ethikkommission Ärztekammer
	Schleswig-Holstein); Hamburg (Ethikkommission Ärztekammer Hamburg); MHH
	Hannover/Coppenbrügge (MHH Ethikkommission); Heidelberg Thorax/Uniklinik
	(Ethikkommission Universität Heidelberg); Homburg (Ethikkommission Saarbrücken);
	Immenhausen (Ethikkommission Landesärztekammer Hessen); Kiel (Ethikkommission
	Christian-Albrechts-Universität zu Kiel); Leipzig (Ethikkommission Universität Leipzig);
	Löwenstein (Ethikkommission Landesärztekammer Baden-Württemberg); Mainz
	(Ethikkommission Landesärztekammer Rheinland-Pfalz); München LMU/Gauting
	(Ethikkommission Klinikum Universität München); Nürnberg (Ethikkommission Friedrich-
	Alexander-Universität Erlangen Nürnberg); Rostock (Ethikkommission Universität
	Rostock); Berchtesgadener Land (Ethikkommission Land Salzburg); Schmallenberg
	(Ethikkommission Arztekammer Westfalen-Lippe); Solingen (Ethikkommission
	Universitat vvitten-Herdecke); Ulm (Etnikkommission Universitat Ulm); Wurzburg
	(Ethikkonninission oniversitat wurzburg). The study was performed in accordance with
	the deciaration of meisting, and an participants gave their written mormed consent.

Study:	ECLIPSE						
Type of study:	COPD-based cohort						
Number of sites:	44 study centers in 12 countries worldwide						
Population:	- 2,164 COPD subjects						
	- 337 smoking controls						
	- 245 nonsmoking controls						
Inclusion Criteria:	COPD						
	 Male/female subjects aged 40–75 years 						
	 Baseline post-bronchodilator FEV₁ of <80% pred and FEV₁/FVC of ≤0.7 						
	 Current or ex-smokers with a smoking history of ≥10 pack-years consent obtained 						
	prior to participation						
	- Ability to comply with the requirements of the protocol and be available for study visits						
	over 3 years						
	CONTROLS - Male/female subjects aged 40–75 years, who are free from significant disease as determined by history, physical examination, and screening investigations - Baseline post-bronchodilator FEV1 of >85% pred and FEV1/FVC of >0.7 - Signed and dated written informed consent obtained prior to participation - Ability to comply with the requirements of the protocol and be available for study visits over 3 years - Current or ex-smokers with a smoking history ≥10 pack-years, or nonsmokers with a smoking history of <1 pack-years						
Exclusion Criteria:	 Known respiratory disorders other than COPD and severe α1-antitrypsin deficiency Prior medical history (known history of significant inflammatory disease other than COPD 						
	 COPD exacerbation within 4 weeks of enrolment Lung surgery 						

	- Recent diagnosis of cancer					
	 Blood transfusion in the 4 weeks prior to study start 					
	- Inability to walk					
	- Taking part in a blinded drug study					
	- Therapy with oral corticosteroids at inclusion					
	 Participation in studies with radiation exposure. 					
Ethics committee	ECLIPSE complies with the Declaration of Helsinki and Good Clinical Practice					
	Guidelines, and has been approved by the ethics committees of the participating					
	centres. All participants provided written informed consent (ClinicaltTrials.gov identifier:					
	NCT00292552). The members of the Evaluation of COPD Longitudinally to Identify					
	Predictive Surrogate End-points (ECLIPSE) Steering Committee are: (University of					
	British Columbia, Vancouver, BC, Canada); (University of Cambridge, Cambridge, UK);					
	(University of Edinburgh, Edinburgh, UK); (Brigham and Women's Hospital, Boston,					
	MA, USA);; (Co-Chair; Hvidovre Hospital, Hvidovre, Denmark); (Son Dureta Hospital					
	and Cimera, Palma, Spain); (University Hospital Aintree, Liverpool, UK); (Caritas St.					
	Elizabeth's Medical Center, Boston, MA, USA); (University of Nebraska, Omaha, NE,					
	USA); (University of Maastricht, Maastricht, the Netherlands)					

Study:	PAC-COPD
Type of study:	COPD-based cohort
Number of sites:	9 tertiary hospital centers in Spain
Population:	329 COPD patients
Inclusion Criteria:	 Patient admitted for the first time for an exacerbation of COPD to any of the 9 participating hospitals between January 2004 and March 2006 (27 months) The diagnosis of COPD is confirmed using spirometric criteria (post-bronchodilation FEV₁/FVC ratio of 0.7) at least 3 months after admission and with the patient in stable condition.
Exclusion Criteria:	 Age under 45 years, Severe comorbidity, such as terminal or advanced cancer, pulmonary tuberculosis with involvement of more than one-third of the total lung parenchyma, pneumectomy, or pneumoconiosis,
	 Old age or general fragility (eg, difficulty walking, lack of autonomy) that can make it substantially difficult for the patient to participate in the study, regardless of the patient's desire to participate,
	- Mental disability diagnosed by the attending physician or determined using the Folstein Mini-Mental State Exam,16 better known as the MiniMental Test in its adapted version validated for Spain17,
	 Not being a resident of the province where the hospital is located, Not being able to understand Spanish.
Ethics committee	 The study was approved by the Ethics Committee of all participating hospitals and the coordinating centre, as detailed below: Comitè Ètic d'Investigació Clínica IMAS: 2004/1762/I, 2002/1346/I Hospital Clínic i Provincial de Barcelona; project approval number: 1215 Hospital de la Santa Creu i Sant Pau, Barcelona; project approval number: 10/05/2002
	 Hospital General Universitari Vall d'Hebron, Barcelona; project approval number: 2002/13461/1
	 Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat; project approval number: 150/02
	 Hospital Universitari Germans Trias i Pujol, Badalona; project approval number: 21/06/2002
	 Hospital de Sabadell, Corporació Parc Taulí, Sabadell; project approval number: 03/141
	 Hospital Son Dureta, Palma de Mallorca; project approval number: 19/06/2002 Hospital de Cruces, Baracaldo, Vizcaya; project approval number: E03/2

Study:	Urban Training
Type of study:	COPD-based cohort
Number of sites:	5 centers in Spain
Population:	407 COPD patients
Inclusion Criteria:	All subjects with a diagnosis of COPD according to the American Thoracic Society/European Respiratory Society recommendations (post-bronchodilator forced expiratory volume in 1 s (FEV ₁) to forced vital capacity (FVC) ratio <0.70) who were seen in any of the participating 33 primary care and five hospital health centers from five Catalan seaside municipalities.
Exclusion Criteria:	Patients with severe or life-threatening comorbidities, or those clinically unstable.

Ethics committee	The Urban Training trial was approved by the Ethics Committees of all participating institutions (Comitè Ètic d'Investigació Clínica Parc de Salut MAR 2011/4291/I, Comitè Ètic d'Investigació Clínica de l'IDIAP Jordi Gol i Gurina P11/116, Comitè Ètic d'Investigació Clínica de l'Hospital Universitari de Bellvitge PR197/11, Comitè Ètic d'Investigació Clínica de l'Hospital Universitari Germans Trias i Pujol AC-12-004, Comitè Ètic d'Investigació Clínica de l'Hospital Clínica de l'Hospital Clínica de Barcelona 2011/7061, Comitè Ètic d'Investigació Clínica de l'Hospital de Mataró November 23rd, 2011) and all participants provided written informed consent.
Study:	OLIN a sterna la se la set
Type of study:	astrima-based conort
Population:	2,055 asthma adults from Northern Sweden recruited by postal questionnaire since
Inclusion Criteria:	- Self-reported asthma
	- Highly suspected asthma
Exclusion Criteria:	No prespecified exclusion criteria.
Ethics committee	Regional Ethical Review Board at Umea University
Study:	U-BIOPRED
Type of study:	asthma-based cohort
Number of sites:	16 clinical centers in 11 European countries
Population:	610 adults with asthma and healthy controls
Inclusion Criteria:	- Severe nonsmoking astimatics,
	- Smokers and ex-smokers with severe asthma, Mild/mederete nen emelving estimation
	- Mild/moderate non-smoking astrimatics,
Evolucion Critoria:	- Healiny holl-shoking controls
Exclusion Onlena.	Approved by the othics committee for each participating clinical institution
	(ClinicalTrials dov identifier: NCT01982162)
Study:	Botterdam Study
Study: Type of study:	Rotterdam Study
Study: Type of study: Number of sites:	Rotterdam Study population-based cohort single-center
Study: Type of study: Number of sites: Population:	Rotterdam Study population-based cohort single-center 14.926 participants
Study: Type of study: Number of sites: Population: Inclusion Criteria:	Rotterdam Study population-based cohort single-center 14,926 participants Inhabitants of the Ommoord district. Rotterdam. Netherlands, aged 45 years or over.
Study: Type of study: Number of sites: Population: Inclusion Criteria: Exclusion Criteria:	Rotterdam Study population-based cohort single-center 14,926 participants Inhabitants of the Ommoord district, Rotterdam, Netherlands, aged 45 years or over. No prespecified exclusion criteria.
Study: Type of study: Number of sites: Population: Inclusion Criteria: Exclusion Criteria: Ethics committee	Rotterdam Study population-based cohort single-center 14,926 participants Inhabitants of the Ommoord district, Rotterdam, Netherlands, aged 45 years or over. No prespecified exclusion criteria. Medical ethics committee of the Erasmus Medical Centre (Rotterdam, the Netherlands), and the review board of the Netherlands Ministry of Health, Welfare and Sports (1068889-159521-PG)
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Data collection, definitions and missing data handling.

An *ad-hoc* data collection form was designed to collect the summary statistics used in this analysis. All data were collected at the index date defined by the first spirometry measurement in the respective cohorts. Comorbidities included hypertension, coronary artery disease (CAD), heart failure, diabetes, depression, gastro-esophageal reflux disease (GERD), osteoporosis, history of stroke, and history of myocardial infarction. Comorbidities were defined based on self-reported doctor diagnosis, validation in medical files, questionnaire-based, or by examination (cfr. below). Underweight = BMI < 18.5, normal weight = BMI \geq 18.5 and < 25, overweight = BMI \geq 25 and < 30, obese = BMI \geq 30. Smoking behavior was self-reported and categorized as current, former, or never smokers. Dyspnea was considered clinically relevant when the mMRC (modified Medical Research Council dyspnea) score \geq 2. Emphysema was defined as per-cohort definition (cfr. below). Chronic bronchitis was defined as daily sputum production lasting for at least three months during two consecutive years. Exacerbations in the year prior to the index data were analyzed and categorized into severe (hospitalization or emergency room visit) and moderate exacerbations (ambulant use of oral corticosteroids and/or antibiotics). Missing data were considered missing at random and were not imputed.

<u>Asthma</u>

- Lifelines: self-reported physician diagnosis
- Rotterdam Study: physician diagnosis in medical files (De Roos EW et al. Respir Med. 2018;139:6-12)
- DTR: self-reported physician diagnosis
- **COSYCONET:** self-reported physician diagnosis
- ECLIPSE: physician diagnosis
- Urban Training: physician diagnosis
- PAC-COPD: physician diagnosis
- U-BIOPRED: "Participants with asthma had either airflow reversibility (increase in forced expiratory volume in 1s (FEV₁) >12% predicted or 200 mL following inhalation of 400 μg salbutamol), airway hyperresponsiveness (methacholine provocative concentration causing a 20% fall in FEV₁ <8 mg·mL-1, or diurnal peak expiratory flow amplitude >8% of mean), or a decrease in FEV₁ of 12% predicted or 200 mL within 4 weeks after tapering maintenance treatment." (Shaw DE, et al. European Respiratory Journal. 2015;46(5):1308-21)
- **OLIN:** physician diagnosis or a medical history of asthma together with a) physiologically verified bronchial variability and/or b) asthma medication.

Emphysema

- **COSYCONET**: self-reported physician-diagnosis
- ECLIPSE: > 5% low attenuation areas (LAA)
- **PAC-COPD:** density < -950 Hounsfield units in at least one are (supracarinal, carinal or infracarinal, in right or left lung)

Hypertension

- Lifelines: self-reported
- Rotterdam Study: use of antihypertensive medication, systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg
- **DTR:** self-reported physician diagnosis
- COSYCONET: self-reported physician diagnosis
- ECLIPSE: self-reported
- Urban Training: physician diagnosis
- PAC-COPD: physician diagnosis

Coronary artery disease

- Lifelines: self-reported
- Rotterdam Study: coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), verified in medical files
- COSYCONET: self-reported physician diagnosis
- ECLIPSE: self-reported

Myocardial infarction

- Lifelines: self-reported
- **DTR:** self-reported physician diagnosis
- COSYCONET: self-reported physician diagnosis
- ECLIPSE: self-reported

Heart failure

- Lifelines: self-reported
- Rotterdam Study: typical symptoms/signs confirmed by radiographic evidence of cardiac dysfunction
- DTR: self-reported physician diagnosis
- COSYCONET: self-reported physician diagnosis
- ECLIPSE: self-reported
- Urban Training: physician diagnosis
- PAC-COPD: physician diagnosis

<u>Stroke</u>

- Lifelines: self-reported
- Rotterdam Study: self-reported and verified in medical files
- DTR: self-reported physician diagnosis
- COSYCONET: self-reported physician diagnosis
- ECLIPSE: self-reported
- **PAC-COPD:** physician diagnosis

Gastro-esophageal reflux disease

- DTR: self-reported physician diagnosis
- COSYCONET: self-reported physician diagnosis
- ECLIPSE: self-reported

Diabetes

- Lifelines: self-reported
- Rotterdam Study: use of blood glucose-lowering medication
- **DTR:** self-reported physician diagnosis
- COSYCONET: self-reported physician diagnosis
- ECLIPSE: self-reported
- Urban Training: physician diagnosis
- PAC-COPD: physician diagnosis

Depression

- Lifelines: self-reported (ever)
- Rotterdam Study: CES-D(20) questionnaire score of 16 or higher
- DTR: self-reported physician diagnosis
- COSYCONET: self-reported physician diagnosis
- ECLIPSE: self-reported

<u>Osteoporosis</u>

- DTR: self-reported
- **COSYCONET:** self-reported physician diagnosis
- ECLIPSE: self-reported

	AO	Total	Proportion (%)	Weight	Weight	Inverse-variance
	n	n	[95%Cl]	(common)	(random)	method
1) Population-based cohorts	5					
Lifelines	572	48,406	1.2 [1.1; 1.3]	75.7%	33.5%	•
DTR	131	9,611	1.4 [1.1; 1.6]	17.3%	33.4%	Œ
Rotterdam Study	53	5,442	1.0 [0.7; 1.3]	7.0%	33.2%	8
Common effect model		63,459	1.2 [1.1; 1.3]	100.0%		1
Random effects model			1.2 [1.0; 1.4]		100.0%	•
Heterogeneity: $I^2 = 56.6\% \tau^2 = < 0$.01, χ ₂ ² :	= 4.61 (p	= 0.10)			
2) Asthma-based cohorts						
OLIN	101	646	15.6 [12.9; 18.7]	67.1%	50.2%	_
U-BIOPRED	51	282	18.1 [13.8; 23.1]	32.9%	49.8%	— — —
Common effect model		928	16.4 [14.2; 18.9]	100.0%		•
Random effects model			16.4 [14.2; 18.9]		100.0%	•
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi_1^2 = 0$	0.86(p	= 0.35)				
3) COPD-based cohorts						
COSYCONET	315	2,599	12.1 [10.9; 13.4]	42.8%	25.5%	<u>₽</u>
ECLIPSE	431	2,075	20.8 [19.0; 22.6]	52.8%	25.5%	-
Urban Training	14	399	3.5 [1.9; 5.8]	2.1%	24.5%	
PAC-COPD	16	329	4.9 [2.8; 7.8]	2.4%	24.6%	│ → —
Common effect model		5,402	15.5 [14.5; 16.6]	100.0%		•
Random effects model			8.5 [3.7; 18.5]		100.0%	
Heterogeneity: $I^2 = 97.6\% \tau^2 = 0.7$	9, χ ₃ ² = ·	126.29(p	< 0.001)			
						0 5 10 15 20 25 30
						Prevalence (%) of AO

Figure S1. Meta-analyzed prevalence of asthma with LLN-defined airflow obstruction.

	AO	FEV₁% pred	FVC% pred	FEV ₁ /FVC %				
	n (%)	mean (95%CI)	mean (95%CI)	mean (95%CI)				
Population coh	orts							
LifeLines	931 (1.9)	88.0 (78.5-97.5)	103.1 (100.7-105.5)	67.5 (58.5-76.5)				
RS	106 (1.9)	82.7 (69.2-96.3)	90.1 (84.1-96.0)	68.1 (58.9-77.4)				
DTR	261 (2.7)	81.1 (68.9-93.4)	88.9 (84.1-93.8)	66.9 (56.9-76.9)				
Asthma cohorts								
OLIN	128 (19.8)	72.9 (45.4-100.3)	81.0 (70.9-91.2)	69.9 (51.1-88.8)				
U-BIOPRED	67 (23.8)	59.2 (36.0-82.4)	85.6 (73.6-97.6)	54.8 (37.0-72.5)				
COPD cohorts								
Urban Training	15 (3.8)	56.4 (53.0-59.9)	77.3 (75.6-79.0)	53.7 (50.8-56.6)				
PAC-COPD	23 (7.0)	51.9 (50.1-53.7)	71.9 (67.9-75.9)	52.8 (51.4-54.2)				
COSYCONET	371 (14.3)	52.5 (51.8-53.3)	78.1 (77.3-78.9)	51.8 (50.8-52.8)				
ECLIPSE	448 (21.6)	44.5 (43.9-45.1)	79.8 (79.0-80.6)	44.4 (43.8-44.9)				

Table S2. Cohort-specific AO prevalence and severity of airflow obstruction.

Table S3. Sample sizes and p-values accompanying Table 1 in the manuscript.

	I	Population co	horts	Asth	ma cohorts	COP	D cohorts
	AO	Asthma- only	COPD- only	AO	Asthma-only	AO	COPD- only
Age (years)		•			•		
N	1298	1985	9760	195	733	857	4088
P-value	REF	0.199	0.016	REF	0.011	REF	0.006
Female							
N	1298	1985	9760	195	733	857	4088
P-value	REF	<0.001	0.053	REF	<0.001	REF	0.121
BMI (kg/m ²)							
N	1298	1983	9755	186	708	857	4086
P-value	REF	<0.001	<0.001	REF	<0.001	REF	0.376
BMI category	1						
N	1298	1982	9755	186	708	857	4086
Underweight P-value	REF	0.060	0.277	REF	0.691	REF	0.801
Normal weight P-value	REF	0.022	0.634	REF	0.017	REF	0.574
<i>Overweight</i> <i>P</i> -value	REF	0.902	0.556	REF	0.898	REF	0.929
<i>Obese</i> <i>P</i> -value	REF	<0.001	0.001	REF	<0.001	REF	0.932
Smoking stat	tus						
N	1283	1971	8430	195	733	856	4085
Never smoker P-value	REF	0.025	0.047	REF	0.289	REF	0.206
Former smoker P-value	REF	0.733	0.318	REF	0.454	REF	0.263

Current smoker P-value	REF	0.001	<0.001	REF	0.039	REF	0.023
Pack-years	•			•			
N	1285	1971	9286	25	90	851	4078
P-value	REF	<0.001	0.050	REF	0.872	REF	0.004
mMRC score	≥2						
N	359	793	2393	128	518	851	4075
P-value	REF	<0.001	<0.001	REF	0.003	REF	0.033
Allergic dise	ase histo	ory					
N	931	1161	7296	195	733	393	2104
P-value	REF	0.644	<0.001	REF	0.588	REF	0.365
Chronic bron	chitis						
N	366	820	2445	195	733	842	3731
P-value	REF	0.017	0.177	REF	0.015	REF	0.446
Emphysema							
N	-	-	-	-	-	828	3523
P-value	REF	NA	NA	REF	NA	REF	0.534
FEV ₁ (%) pres	dicted						
Ν	1197	1840	8627	195	730	857	4088
P-value	REF	<0.001	<0.001	REF	<0.001	REF	0.675
FVC (%) pred	licted						
N	1197	1840	8627	195	730	857	4088
P-value	REF	0.228	<0.001	REF	<0.001	REF	0.987
FEV ₁ /FVC (%)						
N	1298	1985	9760	195	733	857	4088
P-value	REF	<0.001	0.057	REF	<0.001	REF	0.061
Peripheral bl	ood WBC	C (10 ⁹ cells/L)					
N	1018	1546	7988	66	209	471	1864
P-value	REF	0.065	0.515	REF	0.024	REF	0.867
BEC above 3	00 cells/j	μL					
N	895	1124	7055	66	209	459	1864
P-value	REF	<0.001	<0.001	REF	0.112	REF	0.347
Serum CRP (mg/dL)						
N	-	-	-	67	211	21	281
P-value	REF	NA	NA	REF	0.814	REF	0.397
Serum IgE (II	E/mL)						
N	REF	NA	NA	66	209	21	275
P-value	REF	NA	NA	REF	0.760	REF	0.479

AO = asthma with airflow obstruction, BEC = blood eosinophil count, CRP = C-reactive protein, IgE = immunoglobulin E, mMRC = modified Medical Research Council Dyspnea, NA = not applicable, WBC = white blood cell count. AO was defined as ever asthma with airflow obstruction (pre/post BD FEV₁/FVC<0.70) in populationand clinic-based cohorts, respectively. Asthma-only was defined as ever asthma without airflow obstruction and COPD-only was defined as airflow obstruction without a history of asthma. Underweight = BMI < 18.5, normal weight = BMI \ge 18.5 and < 25, overweight = BMI \ge 25 and < 30, obese = BMI \ge 30. Missing variables per cohort: RS and DTR: allergic disease, emphysema, BEC, CRP, IgE; LifeLines: chronic bronchitis, emphysema, mMRC, WBC, CRP, IgE; OLIN: pack-years, chronic bronchitis, WBC, CRP, BEC, IgE; U-BIOPRED: emphysema; COSYCONET: WBC, CRP, BEC, IgE; ECLIPSE: allergic disease history; WBC, CRP, BEC, IgE. Significant differences (P<0.05) with AO are indicated in bold.

Table S4. Meta-analyzed characteristics of LLN-defined AO.

	Рор	ulation-based col	norts	Asthma-ba	sed cohorts	COPD-bas	ed cohorts
	AO	Asthma-only	COPD-only	AO	Asthma-only	AO	COPD-only
Characteristics						·	
Age (years), mean (95% CI)	62.7	63.2	63.6	60.3	59.1	64.7	66.8
	(58.7-66.7)	(57.3-69.2)	(57.8-69.4)	(57.6-63.0)	(56.9-61.4)	(62.9-66.6)	(64.5-69.1)
Female, prop (95% CI)	60.4	60.8	51.5	48.0	58.2	30.7	22.9
	(52.4-68.4)	(54.6-66.9)	(45.3-57.8)	(40.1-55.9)	(54.7-61.6)	(8.1-53.3)	(9.0-36.7)
BMI (kg/m²), mean (95% CI)	26.5	27.6	25.9	26.2	28.2	27.4	27.2
	(26.2-26.8)	(25.9-29.3)	(25.6-26.2)	(23.7-28.8)	(26.1-30.3)	(25.6-29.2)	(26.2-28.2)
Underweight, prop (95% CI)	0.9	0.3	1.6	0.7	1.1	3.6	2.9
	(0.2-1.6)	(0.0-0.7)	(0.1-3.1)	(0.0-2.3)	(0.0-2.6)	(1.4-5.8)	(1.1-4.7)
Normal weight, prop (95% CI)	38.1	32.2	42.1	47.0	27.6	30.5	31.1
	(29.5-46.7)	(21.2-43.1)	(36.8-47.5)	(24.9-69.2)	(21.7-33.6)	(15.2-45.8)	(22.6-39.7)
Overweight, prop (95% CI)	42.9	42.9	42.0	36.3	41.2	36.8	37.2
	(33.1-52.6)	(40.2-45.6)	(35.0-49.0)	(28.5-44.1)	(31.4-51.1)	(33.5-40.2)	(35.5-38.9)
Obese, prop (95% CI)	17.1	25.0	13.5	15.6	30.3	22.4	27.4
	(14.4-19.7)	(11.2-38.7)	(12.3-14.6)	(0.0-37.3)	(13.0-47.7)	(17.3-27.4)	(19.5-35.3)
Never smoker, prop (95% CI)	26.7	31.1	15.2	11.5	25.1	6.3	1.5
	(17.6-35.8)	(20.4-41.9)	(9.3-21.2)	(4.6-18.3)	(0.0-58.2)	(0.0-14.8)	(0.0-3.3)
Former smoker, prop (95% CI)	51.7	52.9	45.7	34.8	36.8	65.4	68.5
	(48.2-55.3)	(47.0-58.9)	(35.5-55.9)	(13.2-56.4)	(33.4-40.2)	(62.0-68.7)	(64.7-72.3)
Current smoker, prop (95% CI)	22.8	15.7	39.1	53.8	38.6	23.5	29.9
	(11.7-34.0)	(3.6-27.9)	(25.6-52.6)	(25.4-82.2)	(2.5-74.7)	(5.4-41.6)	(24.6-35.1)
Pack-years, mean (95% CI)	23.1	19.7	29.9	13.9	18.3	46.3	57.1
	(16.6-29.6)	(13.0-26.3)	(25.6-34.2)	(7.9-20.0)	(14.4-22.2)	(34.0-58.5)	(47.5-66.8)
mMRC score ≥2, prop (95% CI)	41.9	25.2	22.1	60.4	39.8	63.2	59.9
	(34.7-49.1)	(4.4-46.0)	(5.3-39.0)	(50.9-69.9)	(35.7-43.9)	(36.0-90.4)	(34.0-85.7)
Allergic disease history, prop (95% CI)	78.9	40.7	40.8	67.8	73.7	34.4	29.7

	(75.5-82.2)	(38.0-43.4)	(39.1-42.5)	(43.3-92.2)	(62.2-85.1)	(0.0-75.8)	(23.6-35.8)
Chronic bronchitis, prop (95% CI)	28.1	13.9	16.7	30.6	24.0	54.4	53.4
	(11.5-44.6)	(10.1-17.7)	(14.1-19.3)	(0.0-63.7)	(0.7-47.3)	(30.2-78.5)	(35.1-71.6)
Emphysema, prop (95% CI)	-	-	-	-	-	52.1 (2.5-100.0)	47.3 (6.2-88.3)
Spirometry							
FEV ₁ (%) predicted, mean (95% CI)	67.5	88.7	71.8	53.0	78.9	49.6	49.3
	(58.1-76.8)	(81.5-95.9)	(61.7-82.0)	(41.7-64.2)	(63.4-94.5)	(43.0-56.3)	(45.4-53.2)
FVC (%) predicted, mean (95% CI)	90.1	97.6	94.1	77.2	88.7	77.6	76.9
	(79.7-100.6)	(90.8-104.4)	(84.1-104.2)	(73.7-80.8)	(83.2-94.1)	(72.4-82.8)	(73.9-79.8)
FEV ₁ /FVC (%), mean (95% Cl)	57.6	70.6	58.2	53.0	71.7	49.3	48.7
	(54.1-61.0)	(61.4-79.8)	(55.0-61.4)	(38.7-67.3)	(56.3-87.1)	(44.5-54.1)	(44.7-52.8)
Biomarkers							
Peripheral blood WBC (10 ⁹ cells/L),	6.7	6.7	7.3	8.3	7.7	7.9	7.7
mean (95% CI)	(5.8-7.7)	(5.8-7.7)	(5.3-9.3)	(7.6-9.0)	(7.3-8.0)	(7.7-8.1)	(7.3-8.2)
BEC above 300 cells/µL, prop (95% CI)	28.2	16.0	16.0	52.9	35.3	23.7	18.8
	(24.4-31.9)	(14.0-18.1)	(14.7-17.3)	(39.2-66.6)	(29.0-41.5)	(19.7-27.7)	(13.0-24.7)
Serum CRP (mg/dL), median (IQR)*	-	-	-	2.2 (3.5)	2.1 (3.8)	4.3 (5.3)	3.7 (5.2)
Serum IgE (IE/mL), median (IQR)*	-	-	-	116 (292)	110 (221)	83 (208)	54 (119)

AO = asthma with airflow obstruction, BEC = blood eosinophil counts, CRP = C-reactive protein, IgE = immunoglobulin E, mMRC = modified Medical Research Council Dyspnea, WBC = white blood cell count. AO was defined as a physician-diagnosis of asthma (ever) with airflow obstruction (pre/post BD FEV₁/FVC<LLN) in population- and clinic-based cohorts, respectively. Asthma-only was defined as ever asthma without airflow obstruction and COPD-only was defined as airflow obstruction without a history of asthma. Underweight = BMI < 18.5, normal weight = BMI \ge 18.5 and < 25, overweight = BMI \ge 25 and < 30, obese = BMI \ge 30. *Summary statistics of individual cohorts were meta-analyzed, except for IgE and CRP for which only single-study data was available. Missing variables per cohort: Rotterdam Study and DTR: allergic disease, emphysema, BEC, CRP, IgE; LifeLines: chronic bronchitis, emphysema, mMRC, WBC, CRP, IgE; OLIN: pack-years, chronic bronchitis, WBC, CRP, BEC, IgE, emphysema; U-BIOPRED: emphysema; COSYCONET: WBC, CRP, BEC, IgE; ECLIPSE: allergic disease history, CRP, IgE; PAC-COPD: no missing variables; Urban Training: chronic bronchitis, emphysema, allergic disease history; WBC, CRP, BEC, IgE. Significant differences (*P*<0.05) with AO are indicated in bold.

	FR-based of	obstruction	LLN-based	obstruction
	Normal	AO	Normal	AO
	(n = 4132)	(n = 106)	(n = 4613)	(n = 53)
Age (years), mean (SD)	68.8 (8.8)	67.8 (8.0)	69.2 (8.9)	65.7 (8.1)
Female, n (%)	2352 (56.9)	63 (59.4)	2540 (55.1)	38 (71.7)
BMI (kg/m²), mean (SD)	27.7 (4.3)	26.9 (5.1)	27.5 (4.3)	26.2 (4.6)
Underweight, n (%)	13 (0.3)	1 (0.9)	16 (0.3)	1 (1.9)
Normal weight, n (%)	1102 (26.7)	46 (43.4)	1268 (27.5)	27 (50.9)
Overweight, n (%)	2025 (49.0)	37 (34.9)	2257 (48.9)	16 (30.2)
Obese, n (%)	991 (24.0)	22 (20.8)	1071 (23.2)	9 (17.0)
Never smoker, n (%)	1521 (36.8)	34 (32.1)	1626 (35.2)	16 (30.2)
Former smoker, n (%)	2209 (53.5)	59 (55.7)	2487 (53.9)	26 (49.1)
Current smoker, n ()	401 (9.7)	13 (12.3)	500 (10.8)	11 (20.8)
Pack-years, mean (SD)	12.1 (18.0)	18.0 (23.4)	13.3 (19.1)	18.7 (25.9)
mMRC score ≥2, n (%)	340 (8.9)	47 (48.0)	415 (9.8)	22 (45.8)
Chronic bronchitis, n (%)	151 (3.7)	16 (15.2)	196 (4.3)	10 (19.2)
FEV ₁ (%) predicted, mean (SD)	101.7 (15.7)	74.2 (16.7)	99.9 (16.5)	66.0 (14.1)
FVC (%) predicted, mean (SD)	99.5 (15.1)	89.6 (16.0)	99.1 (15.4)	85.5 (14.4)
FEV ₁ /FVC (%), mean (SD)	78.7 (4.8)	63.5 (6.1)	77.5 (5.8)	59.6 (6.4)
Peripheral blood WBC (10 ⁹ cells/L), mean (SD)	7.0 (1.9)	7.3 (1.5)	7.0 (1.9)	7.2 (1.4)

Table S5. Characteristics of AO compared to normal group in the Rotterdam Study.

AO = asthma with airflow obstruction; FR = fixed ratio (FEV₁/FVC < 0.7); LLN = lower limit of normal (FEV₁/FVC < LLN); normal = no asthma nor COPD. Underweight = BMI < 18.5, normal weight = BMI ≥ 18.5 and < 25, overweight = BMI ≥ 25 and < 30, obese = BMI ≥ 30. Significant differences (P<0.05) indicated in bold.

Table S6. Exacerbation rate in last year of AO in clinic-based cohorts.

ECLIPSE	FR-based obstru	iction	LLN-based obstruction			
	AO vs COPD-only OR (95%CI)	P-value	AO vs COPD-only OR (95%CI)	P-value		
1 or more moderate exacerbations	1.76 (1.44-2.15)	<0.01	1.71 (1.34-2.18)	<0.01		

U-BIOPRED	FR-based obstru	ction	LLN-based obstru	uction
	AO vs asthma-only OR (95%CI)	P-value	AO vs asthma-only OR (95%CI)	P-value
1 or more moderate exacerbations	2.05 (1.01-4.17)	0.05	1.60 (0.75-3.42)	0.23

COSYCONET	FR-ba	ased obstructio	n	LLN-based obstruction					
	AO	COPD-only	P-	AO	COPD-only	P-			
	n (%)	n (%)	value	n (%)	n (%)	value			
1 or more moderate exacerbations	148 (39.9%)	495 (27.3%)	<0.01	130 (41.3%)	441 (28.4%)	<0.01			
1 or more severe exacerbations	85 (22.9%)	357 (19.7%)	<0.01	78 (24.8%)	326 (21.0%)	0.16			

AO = asthma with airflow obstruction; FR = fixed ratio (FEV1/FVC < 0.7); LLN = lower limit of normal (FEV1/FVC < LLN); OR = odds ratio. Odds ratios were adjusted for age, sex, smoking status, and BMI.



Figure S2.1. Meta-analyzed (adjusted odds) of osteoporosis.



Figure S2.2. Meta-analyzed (adjusted odds) of gastro-esophageal reflux disease.

	OR	95%-Cl			IV, C	Com	mon		
AO vs asthma-only (general population)									
LifeLines	2.00	[0.93; 4.27]				+			
Danish Twin Registry									
Rotterdam Study	2.17	[1.10; 4.27]				-	-		
Common effect model	2.09	[1.26; 3.47]						-	
Random effects model	2.09	[1.26; 3.47]						-	
Heterogeneity: $J^2 = 0\%$, $\tau^2 = 0$, $\chi_1^2 = 0.02 (p = 0.88)$									
AO vs COPD-only (general population)									
LifeLines	1.49	[0.92; 2.39]				+			
Danish Twin Registry									
Rotterdam Study	2.59	[1.40; 4.78]							
Common effect model	1.83	[1.26; 2.67]							
Random effects model	1.89	[1.10; 3.24]				-		-	
Heterogeneity: $l^2 = 49\%$, $\tau^2 = 0.08$, $\chi_1^2 = 1.96$ ($p = 0$.16)								
AO vs COPD-only (clinic-based)									
COSYCONET	0.98	[0.71; 1.36]				-0	-		
ECLIPSE	0.84	[0.54; 1.30]					-		
Urban Training									
PAC-COPD									
Common effect model	0.93	[0.71; 1.21]				+			
Random effects model	0.93	[0.71; 1.21]				+			
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi_1^2 = 0.3$ ($p = 0.58$)			_						
				1		1	1	-	1
			0.1	0.2	0.5	1	2	_ 5	10
				0	dds ra	atio	tor CA	Ð	

Figure S2.3. Meta-analyzed (adjusted odds) of coronary artery disease.

	OR	95%-CI			IV, C	om	mon		
AO vs asthma-only (general population	1)								
LifeLines	0.97	[0.74; 1.27]				+			
Danish Twin Registry	0.78	[0.51; 1.20]				╸			
Rotterdam Study	0.99	[0.60; 1.63]			_		_		
Common effect model	0.93	[0.75; 1.14]				+			
Random effects model	0.93	[0.75; 1.14]				+			
Heterogeneity: $J^2 = 0\%$, $\tau^2 = 0$, $\chi_2^2 = 0.81$ ($p = 0.6$	67)								
AO vs COPD-only (general population)									
LifeLines	1.41	[1.14; 1.74]				-	+		
Danish Twin Registry	1.47	[1.03; 2.10]							
Rotterdam Study	1.31	[0.81; 2.13]					—		
Common effect model	1.41	[1.19; 1.67]				_ ◀	►		
Random effects model	1.41	[1.19; 1.67]				•	►		
Heterogeneity: $J^2 = 0\%$, $\tau^2 = 0$, $\chi_2^2 = 0.14$ ($p = 0.5$	93)								
AO vs COPD-only (clinic-based)									
COSYCONET	1.40	[1.06; 1.83]					+		
ECLIPSE	0.50	[0.26; 0.95]		-		-			
Urban Training									
PAC-COPD									
Common effect model	1.20	[0.93; 1.54]				•	►		
Random effects model	0.87	[0.32; 2.38]							
Heterogeneity: J^2 = 88%, τ^2 = 0.46, χ_1^2 = 8.24 (p	< 0.01)		_						
						Т			
			0.1	0.2	0.5	1	2	5	10
				Odd	s ratio	for c	lepre	ssion	1

Figure S2.4. Meta-analyzed (adjusted odds) of depression.



Figure S2.5. Meta-analyzed (adjusted odds) of hypertension.

	OR	95%-Cl			IV, C	Com	non		
AO vs asthma-only (general population)									
LifeLines	0.47	[0.31; 0.72]							
Danish Twin Registry	1.09	[0.54; 2.20]				-			
Rotterdam Study	0.97	[0.52; 1.84]							
Common effect model	0.66	[0.49; 0.90]			-	►			
Random effects model	0.75	[0.43; 1.31]							
Heterogeneity: $J^2 = 66\%$, $\tau^2 = 0.15$, $\chi_2^2 = 5.9$ ($p = 0$.	05)								
AO vs COPD-only (general population)									
LifeLines	0.85	[0.60; 1.21]			_				
Danish Twin Registry	1.61	[0.92; 2.82]				+			
Rotterdam Study	0.93	[0.51; 1.71]					_		
Common effect model	1.00	[0.77; 1.31]				\blacklozenge			
Random effects model	1.05	[0.71; 1.54]				\blacklozenge	•		
Heterogeneity: $J^2 = 45\%$, $\tau^2 = 0.05$, $\chi^2_2 = 3.63$ ($p = 0.05$)).16)								
AO vs COPD-only (clinic-based)									
COSYCONET	1.30	[0.92; 1.83]				┼ि	-		
ECLIPSE	0.96	[0.46; 1.98]							
Urban Training	1.01	[0.31; 3.22]				-		-	
PAC-COPD	0.18	[0.02; 1.36]	~	•					
Common effect model	1.16	[0.86; 1.57]				+	•		
Random effects model	1.16	[0.86; 1.57]				+	•		
Heterogeneity: $J^2 = 25\%$, $\tau^2 = < 0.01$, $\chi_3^2 = 4.01$ (p =	= 0.26)		_						
			I	1	1	I	1	I	1
			0.1	0.2	0.5	1	2	5	10
				Od	ds rati	o for	diab	etes	

Figure S2.6. Meta-analyzed (adjusted odds) of diabetes mellitus type 2.

	OR	95%-Cl			IV, C	Com	non		
AO vs asthma-only (general population)						Ι			
LifeLines	1.27	[0.67; 2.42]			-		<u> </u>		
Danish Twin Registry	0.60	[0.27; 1.31]		_	+	—			
Rotterdam Study	0.51	[0.10; 2.50]	_			_			
Common effect model	0.89	[0.55; 1.43]					•		
Random effects model	0.84	[0.45; 1.58]					-		
Heterogeneity: $l^2 = 25\%$, $\tau^2 = 0.10$, $\chi^2_2 = 2.66$ ($p = 0$	0.26)								
AO vs COPD-only (general population)									
LifeLines	1.18	[0.75; 1.86]							
Danish Twin Registry	0.86	[0.46; 1.61]					-		
Rotterdam Study	0.34	[0.07; 1.57]	←		0	_	-		
Common effect model	0.99	[0.69; 1.42]			-	\blacklozenge	•		
Random effects model	0.99	[0.69; 1.42]			-	\blacklozenge	•		
Heterogeneity: $l^2 = 24\%$, $\tau^2 = < 0.01$, $\chi_2^2 = 2.64$ (p =	= 0.27)								
AO vs COPD-only (clinic-based)									
COSYCONET	1.30	[0.78; 2.17]				-+0	_		
ECLIPSE	0.43	[0.27; 0.71]		_					
Urban Training	1.76	[0.21; 14.97]				_	•		\rightarrow
PAC-COPD	1.72	[0.34; 8.62]				_	-8		_
Common effect model	0.78	[0.55; 1.09]							
Random effects model	0.93	[0.42; 2.03]							
Heterogeneity: $l^2 = 72\%$, $\tau^2 = 0.36$, $\chi_3^2 = 10.83$ (p =	0.01)		_						_
			1	1		1	1	_	1
			0.1	0.2	0.5	1	2	5	10
				Odds	ratio	tor h	eart f	ailure	

Figure S2.7. Meta-analyzed (adjusted odds) of heart failure.

	OR	95%-Cl			IV,	Com	mon		
AO vs asthma-only (general population)									
LifeLines	1.38	[0.76; 2.51]				-+6	•		
Danish Twin Registry	1.03	[0.42; 2.51]							
Rotterdam Study									
Common effect model	1.26	[0.77; 2.07]							
Random effects model	1.26	[0.77; 2.07]							
Heterogeneity: $J^2 = 0\%$, $\tau^2 = 0$, $\chi_1^2 = 0.29$ ($p = 0.59$)									
AO vs COPD-only (general population)									
LifeLines	1.00	[0.68; 1.47]				-0	-		
Danish Twin Registry	0.82	[0.43; 1.57]					_		
Rotterdam Study									
Common effect model	0.95	[0.68; 1.33]				+	•		
Random effects model	0.95	[0.68; 1.33]				+	•		
Heterogeneity: $J^2 = 0\%$, $\tau^2 = 0$, $\chi_1^2 = 0.27$ ($p = 0.60$)									
AO vs COPD-only (clinic-based)									
COSYCONET	1.04	[0.68; 1.60]				- ₽	_		
ECLIPSE	0.33	[0.19; 0.57]			+				
Urban Training									
PAC-COPD									
Common effect model	0.67	[0.48; 0.95]							
Random effects model	0.60	[0.19; 1.83]							
Heterogeneity: $I^2 = 90\%$, $\tau^2 = 0.59$, $\chi_1^2 = 10.33$ (p <	0.01)		_						
			1			і	-	 _	1
			0.1	0.2	0.5	1	2	5	10
			Odd	ls rati	o for i	myoc	cardial	ınfar	ction

Figure S2.8. Meta-analyzed (adjusted odds) of myocardial infarction history.

	OR	95%-Cl			IV, C	ommo	on		
AO vs asthma-only (general population)						1			
LifeLines	0.99	[0.47; 2.08]				<u> </u>	-		
Danish Twin Registry	0.53	[0.23; 1.23]				+			
Rotterdam Study	4.85	[1.13; 20.75]						-	→
Common effect model	0.95	[0.57; 1.60]							
Random effects model	1.19	[0.38; 3.76]							
Heterogeneity: $I^2 = 70\%$, $\tau^2 = 0.76$, $\chi^2_2 = 6.71$ ($p = 0$).03)								
AO vs COPD-only (general population)									
LifeLines	0.95	[0.56; 1.61]			_	•			
Danish Twin Registry	0.71	[0.35; 1.44]				+-			
Rotterdam Study	1.50	[0.54; 4.20]							
Common effect model	0.93	[0.63; 1.37]							
Random effects model	0.93	[0.63; 1.37]				•			
Heterogeneity: $J^2 = 0\%$, $\tau^2 = 0$, $\chi_2^2 = 1.4$ ($p = 0.50$)									
AO vs COPD-only (clinic-based)									
COSYCONET	0.89	[0.49; 1.61]							
ECLIPSE	0.45	[0.23; 0.86]			•	-			
Urban Training									
PAC-COPD	1.18	[0.14; 9.69]							_
Common effect model	0.67	[0.44; 1.03]				►			
Random effects model	0.67	[0.37; 1.22]				•			
Heterogeneity: $l^2 = 24\%$, $\tau^2 = 0.10$, $\chi^2_2 = 2.63$ ($p = 0$).27)								_
			1	1	1	I	-	I	I
			0.1	0.2	0.5	1 2	2	5	10
				Oc	lds rati	o for s	stroke		

Figure S2.9. Meta-analyzed (adjusted odds) of stroke history.

	AO vs asthma-only		AO vs COPD-	only	
	OR (95%CI)	P-value	OR (95%CI)	P-value	
DTR (population-	based cohort)				
Osteoporosis	1.22 (0.67-2.21)	0.52	2.30 (1.43-3.72)	<0.01	
GERD	0.83 (0.48-1.44)	0.50	1.68 (1.06-2.68)	0.03	
U-BIOPRED (clini	c-based cohort)				
Osteoporosis	1.38 (0.74-2.60)	0.31	NA	NA	
GERD	0.80 (0.45-1.43)	0.45	NA	NA	
CAD	2.03 (0.61-6.71)	0.25	NA	NA	
Depression	0.88 (0.28-2.81)	0.84	NA	NA	
Hypertension	0.76 (0.41-1.41)	0.39	NA	NA	
Diabetes	0.92 (0.37-2.26)	0.86	NA	NA	

Table S7. Adjusted odds ratio for comorbidities which could not be meta-analyzed.

CAD = coronary artery disease; DTR = the Danish Twin Registry; GERD = gastro-esophageal reflux disease. Osteoporosis and GERD were not meta-analyzed as only data from DTR was available for population-based cohorts. Comorbidities in asthma-based cohorts were not meta-analyzed as only data from U-BIOPRED was available. Logistic regression models adjusted for age, sex, smoking status, and body mass index. Significant differences (*P*<0.05) are indicated in bold.

Table S8. Comorbidities	verified by	examinations	or	validated	in	medical	files	in	the
Rotterdam Study.	-								

	AO vs Asthma-only	AO vs COPD-only
	OR (95% CI)	OR (95% CI)
Hypertension	0.83 (0.47-1.45)	0.80 (0.49-1.32)
Coronary artery disease	2.17 (1.10-4.27)	2.59 (1.40-4.78)
Heart failure	0.51 (0.10-2.50)	0.34 (0.07-1.57)
Stroke history	4.85 (1.13-20.75)	1.50 (0.54-4.20)
Depression	0.99 (0.60-1.63)	1.31 (0.81-2.13)

	Comorbidity n	Patients n	Proportion (%) [95%Cl]		Inver	se-varia method	ance	
Patients with AO (clinic-based)								
COSYCONET	89	371	24.0 [19.7; 28.7]				<u> </u>	
ECLIPSE	82	412	19.9 [16.2; 24.1]					
Urban Training	3	15	20.0 [4.3; 48.1]	-		•		<i></i>
Common effect model		798	21.9 [19.1; 24.9]			-		
Random effects model			21.8 [18.3; 25.8]			-	-	
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0.01$, $\chi^2_2 = 1.94$ ($p = 0.3$	38)							
Patients with COPD-only (clinic-based)								
COSYCONET	255	1,810	14.1 [12.5; 15.8]		+	}		
ECLIPSE	198	1,524	13.0 [11.3; 14.8]					
Urban Training	41	357	11.5 [8.4; 15.3]					
Common effect model		3,691	13.4 [12.3; 14.5]		•			
Random effects model			13.4 [12.3; 14.5]		•			
Heterogeneity: $J^2 = 4\%$, $\tau^2 = < 0.01$, $\chi^2_2 = 2.08$ (p = 0	0.35)							
				0	10	20	30	40
				Prev	alence	(%) of o	steopor	osis

Figure S3.1. Meta-analyzed (prevalence) of osteoporosis.



Figure S3.2. Meta-analyzed (prevalence) of gastro-esophageal reflux disease.

	Comorbidity n	Patients n	Proportion (%) [95%Cl]	Inverse-variance method
Patients with AO (general population)				
Rotterdam Study	18	105	17.1 [10.5; 25.7]	
Lifelines	21	931	2.3 [1.4; 3.4]	
Common effect model		1,036	5.5 [4.0; 7.5]	•
Random effects model			6.4 [0.8; 37.1]	
Heterogeneity: $l^2 = 98\%$, $\tau^2 = 2.35$, $\chi_1^2 = 41.56 (p < 0.01)$				
Patients with COPD-only (general population)				
Rotterdam Study	94	789	11.9 [9.7; 14.4]	
Lifelines	122	7,296	1.7 [1.4; 2.0]	•
Common effect model		8,085	3.8 [3.3; 4.4]	•
Random effects model			4.6 [0.6; 26.8]	
Heterogeneity: $l^2 = 100\%$, $\tau^2 = 2.14$, $\chi_1^2 = 210.63(p < 0.01)$				
Patients with asthma-only (general population)				
Rotterdam Study	39	410	9.5 [6.9; 12.8]	
Lifelines	12	1,161	1.0 [0.5; 1.8]	Œ
Common effect model		1,571	5.6 [4.2; 7.3]	•
Random effects model			3.2 [0.3; 24.4]	
Heterogeneity: $J^2 = 98\%$, $\tau^2 = 2.61$, $\chi_1^2 = 47.38(p < 0.01)$				
Patients with AO (clinic-based)				
COSYCONET	53	370	14.3 [10.9; 18.3]	
ECLIPSE	51	419	12.2 [9.2; 15.7]	
Urban Training	0	15	0.0 [0.0; 21.8]	<u> </u>
Common effect model		804	13.1 [10.9; 15.7]	•
Random effects model			13.1 [10.9; 15.7]	•
Heterogeneity: $J^2 = 0\%$, $\tau^2 = < 0.01$, $\chi^2_2 = 1.95$ ($p = 0.38$)				
Patients with COPD-only (clinic-based)				
COSYCONET	308	1,810	17.0 [15.3; 18.8]	<u>₩</u>
ECLIPSE	163	1,535	10.6 [9.1; 12.3]	- - •
Urban Training	36	351	10.3 [7.3; 13.9]	
Common effect model		3,696	14.0 [12.9; 15.2]	•
Random effects model			12.5 [8.9; 17.3]	
Heterogeneity: $J^2 = 94\%$, $\tau^2 = 0.10$, $\chi_2^2 = 32.11$ ($p < 0.01$)				
				0 10 20 30 40 Prevalence (%) of CAD

Figure S3.3. Meta-analyzed (prevalence) of coronary artery disease.

	Comorbidity n	Patients n	Proportion (%) [95%Cl]	Inverse-variance method
Patients with AO (general population)				1
Rotterdam Study	29	98	29.6 [20.8: 39.7]	
Lifelines	120	931	12.9 [10.8: 15.2]	—
Danish Twin Registry	47	261	18.0 [13.5: 23.2]	
Common effect model		1.290	15.6 [13.7: 17.7]	•
Random effects model		-,	18.9 [11.5: 29.5]	
Heterogeneity: $J^2 = 90\%$, $\tau^2 = 0.24$, $\chi^2_2 = 20.1$ ($p < 0.01$)				
Patients with COPD-only (general population)				
Rotterdam Study	179	757	23.6 [20.7; 26.8]	- 8 -
Lifelines	680	7,296	9.3 [8.7; 10.0]	+
Danish Twin Registry	210	1,650	12.7 [11.2; 14.4]	
Common effect model		9,703	11.4 [10.8; 12.1]	•
Random effects model			14.3 [8.1; 23.9]	
Heterogeneity: $J^2 = 99\%$, $\tau^2 = 0.31$, $\chi^2_2 = 139.41 (p < 0.01)$				
Patients with asthma-only (general population)				
Rotterdam Study	127	391	32.5 [27.9; 37.4]	
Lifelines	166	1,161	14.3 [12.3; 16.4]	
Danish Twin Registry	86	409	21.0 [17.2; 25.3]	— <u>—</u>
Common effect model		1,961	20.2 [18.4; 22.1]	◆
Random effects model			21.7 [13.1; 33.6]	
Heterogeneity: $J^2 = 97\%$, $\tau^2 = 0.27$, $\chi_2^2 = 60.25$ ($p < 0.01$)				
Patients with AO (clinic-based)				
COSYCONET	98	371	26.4 [22.0; 31.2]	
ECLIPSE	103	433	23.8 [19.9; 28.1]	
Urban Training	0	15	0.0 [0.0; 21.8]	
Common effect model		819	24.9 [22.0; 28.0]	•
Random effects model			24.9 [22.0; 28.0]	•
Heterogeneity: $J^2 = 41\%$, $\tau^2 = < 0.01$, $\chi_2^2 = 3.37$ ($p = 0.19$)				
Patients with COPD-only (clinic-based)				
COSYCONET	342	1,811	18.9 [17.1; 20.8]	
ECLIPSE	230	1,599	14.4 [12.7; 16.2]	
Urban Training	17	351	4.8 [2.8; 7.6]	
Common effect model		3,761	16.3 [15.1; 17.5]	•
Random effects model			11.5 [5.1; 23.8]	
Heterogeneity: $I^2 = 95\%$, $\tau^2 = 0.58$, $\chi_2^2 = 42.26 (p < 0.01)$				
				U U $2U$ $3U$ $4U$
				Fievalence (%) of depression

Figure S3.4. Meta-analyzed (prevalence) of depression.

	Comorbidity	Patients	Proportion (%)	Inv	erse-var	iance	
	n	n	[95%CI]		metho	a	
Patients with AO (general population)							
Rotterdam Study	71	106	67.0 [57.2; 75.8]		-		
Lifelines	348	928	37.5 [34.4; 40.7]		+		
Danish Twin Registry	100	261	38.3 [32.4; 44.5]				
Common effect model		1,295	39.9 [37.2; 42.6]		•		
Random effects model			47.2 [29.4; 65.8]	-		-	
Heterogeneity: $J^2 = 94\%$, $\tau^2 = 0.44$, $\chi^2_2 = 31.75(p < 0.01)$							
Patients with COPD-only (general population)							
Rotterdam Study	597	791	75.5 [72.3; 78.4]			-8-	
Lifelines	2,364	6,794	34.8 [33.7; 35.9]		+		
Danish Twin Registry	519	1,661	31.2 [29.0; 33.5]	ŧ	8		
Common effect model		9,246	37.0 [36.0; 38.1]		•		
Random effects model			47.5 [21.4; 75.0]	-			
Heterogeneity: $l^2 = 100\% \tau^2 = 1.12, \chi_2^2 = 439.28 (p < 0.01)$							
Patients with asthma-only (general population)							
Rotterdam Study	320	413	77.5 [73.1; 81.4]				
Lifelines	454	1,161	39.1 [36.3; 42.0]		+		
Danish Twin Registry	144	410	35.1 [30.5; 40.0]				
Common effect model		1,984	44.9 [42.6; 47.2]		•		
Random effects model			51.4 [25.0; 77.0]				
Heterogeneity: $J^2 = 99\%$, $\tau^2 = 1.03$, $\chi^2_2 = 180.82(p < 0.01)$							
Patients with AO (clinic-based)							
COSYCONET	202	371	54.4 [49.2; 59.6]				
ECLIPSE	186	429	43.4 [38.6; 48.2]				
Urban Training	9	15	60.0 [32.3; 83.7]				
PAC-COPD	5	23	21.7 [7.5; 43.7]				
Common effect model		838	48.1 [44.7; 51.6]		•		
Random effects model			45.6 [32.5; 59.3]				
Heterogeneity: $J^2 = 82\%$, $\tau^2 = 0.23$, $\chi_3^2 = 16.33$ ($p < 0.01$)							
Patients with COPD-only (clinic-based)							
COSYCONET	1,034	1,811	57.1 [54.8; 59.4]		÷		
ECLIPSE	656	1,559	42.1 [39.6; 44.6]		•		
Urban Training	174	351	49.6 [44.2; 54.9]				
PAC-COPD	110	292	37.7 [32.1; 43.5]				
Common effect model		4,013	49.2 [47.7; 50.8]		•		
Random effects model			46.7 [38.4; 55.2]		•		
Heterogeneity: $J^2 = 97\%$, $\tau^2 = 0.11$, $\chi_3^2 = 91.47 (p < 0.01)$							
				0 00	10 0		40
				U 20 Drevelation	40 6	U 80	10 aiar
				rievalenc	/e (%)0⊺I	iyperien	SION

Figure S3.5. Meta-analyzed (prevalence) of hypertension.

100

	Comorbidity n	Patients n	Proportion (%) [95%Cl]	Inverse-variance method
Patients with AO (general population)				1
Rotterdam Study	16	104	15.4 [9.1: 23.8]	
Lifelines	40	929	4.3 [3.1: 5.8]	
Danish Twin Registry	18	261	69[41.107]	
Common effect model		1 294	63[50:78]	
Random effects model		1,204	76[36:155]	-
Heterogeneity: $J^2 = 90\%$, $\tau^2 = 0.45$, $\chi^2_2 = 19.73$ ($p < 0.01$)			1.0 [0.0, 10.0]	
Patients with COPD-only (general population)				
Rotterdam Study	138	778	17.7 [15.1; 20.6]	_
Lifelines	372	7,283	5.1 [4.6; 5.6]	+
Danish Twin Registry	73	1,656	4.4 [3.5; 5.5]	⊕
Common effect model		9,717	6.6 [6.1; 7.2]	•
Random effects model			7.5 [3.0; 17.5]	
Heterogeneity: $J^2 = 99\%$, $\tau^2 = 0.71$, $\chi^2_2 = 180.14(p < 0.01)$				
Patients with asthma-only (general population)				
Rotterdam Study	79	406	19.5 [15.7; 23.6]	— <u>—</u>
Lifelines	98	1,154	8.5 [6.9; 10.3]	
Danish Twin Registry	27	410	6.6 [4.4; 9.4]	
Common effect model		1,970	11.2 [9.8; 12.7]	•
Random effects model			10.5 [5.4; 19.6]	
Heterogeneity: $l^2 = 95\%$, $\tau^2 = 0.40$, $\chi_2^2 = 43.85(p < 0.01)$				
Patients with AO (clinic-based)				
COSYCONET	57	371	15.4 [11.8; 19.4]	_
ECLIPSE	45	438	10.3 [7.6; 13.5]	
Urban Training	5	15	33.3 [11.8; 61.6]	
PAC-COPD	1	22	4.5 [0.1; 22.8]	
Common effect model		846	13.2 [11.0; 15.7]	▲
Random effects model			14.3 [8.2; 23.8]	
Heterogeneity: $J^2 = 72\%$, $\tau^2 = 0.26$, $\chi_3^2 = 10.77$ ($p = 0.01$)				
Patients with COPD-only (clinic-based)				
COSYCONET	239	1,810	13.2 [11.7; 14.9]	
ECLIPSE	170	1,595	10.7 [9.2; 12.3]	
Urban Training	101	351	28.8 [24.1; 33.8]	
PAC-COPD	60	292	20.5 [16.1; 25.6]	
Common effect model		4,048	14.7 [13.6; 15.8]	♦
Random effects model			17.2 [10.8; 26.2]	
Heterogeneity: $l^2 = 96\%$, $\tau^2 = 0.29$, $\chi_3^2 = 83.84$ ($p < 0.01$)				
				0 10 20 30 40
				Prevalence (%) of diabetes

Figure S3.6. Meta-analyzed (prevalence) of diabetes mellitus type 2.

	Comorbidity	Patients	Proportion (%)	Inverse-variance
	n	n	[95%CI]	method
Patients with $\Delta \Omega$ (general population)				
Rotterdam Study	2	105	19[0.2.67]	
Lifelines	23	919	25[16:37]	
Danish Twin Registry	12	261	46[24:79]	
Common effect model	12	1 285	30[22:41]	
Random effects model		1,200	3 1 [1 9: 5 0]	
Heterogeneity: $J^2 = 42\%$, $\tau^2 = 0.09$, $\chi^2_2 = 3.46$ ($p = 0.18$)			0.1 [1.0, 0.0]	
Patients with COPD-only (general population)				
Rotterdam Study	53	789	6.7 [5.1; 8.7]	- B -
Lifelines	163	7,199	2.3 [1.9; 2.6]	•
Danish Twin Registry	92	1,673	5.5 [4.5; 6.7]	—
Common effect model		9,661	3.5 [3.2; 4.0]	•
Random effects model			4.4 [2.2; 8.3]	-
Heterogeneity: $J^2 = 97\%$, $\tau^2 = 0.35$, $\chi^2_2 = 74.65$ ($p < 0.01$)				
Patients with asthma-only (general population)				
Rotterdam Study	18	410	4.4 [2.6; 6.8]	
Lifelines	22	1,141	1.9 [1.2; 2.9]	⊞
Danish Twin Registry	22	409	5.4 [3.4; 8.0]	
Common effect model		1,960	3.5 [2.7; 4.5]	•
Random effects model			3.6 [1.9; 6.6]	◆
Heterogeneity: $J^2 = 85\%$, $\tau^2 = 0.27$, $\chi^2_2 = 13.25$ ($p < 0.01$)				
Patients with AO (clinic-based)				
COSYCONET	21	369	5.7 [3.6; 8.6]	
ECLIPSE	25	421	5.9 [3.9; 8.6]	
Urban Training	1	15	6.7 [0.2; 31.9]	•
PAC-COPD	2	22	9.1 [1.1; 29.2]	
Common effect model		827	5.9 [4.5; 7.8]	◆
Random effects model			5.9 [4.5; 7.8]	◆
Heterogeneity: $J^2 = 0\%$, $\tau^2 = 0$, $\chi_3^2 = 0.44$ ($p = 0.93$)				
Patients with COPD-only (clinic-based)				
COSYCONET	93	1,811	5.1 [4.2; 6.3]	
ECLIPSE	116	1,578	7.4 [6.1; 8.8]	
Urban Training	13	351	3.7 [2.0; 6.3]	-
PAC-COPD	16	292	5.5 [3.2; 8.7]	- e
Common effect model		4,032	6.0 [5.3; 6.8]	•
Random effects model			5.6 [4.2; 7.3]	◆
Heterogeneity: $I^2 = 72\%$, $\tau^2 = 0.05$, $\chi_3^2 = 10.83$ ($p = 0.01$)				
				U = 10 = 20 = 30 = 40
				Prevalence (%) of neart failure

Figure S3.7. Meta-analyzed (prevalence) of heart failure.

	Comorbidity	Patients	Proportion (%)	Inverse-variance
	n	n	[95%CI]	method
Patients with AQ (general population)				
Lifelines	32	927	3.5 [2.4: 4.8]	
Danish Twin Registry	11	260	4 2 [2 1 7 4]	
Common effect model		1 187	36[27:49]	
Random effects model		.,	3.6 [2.7: 4.9]	•
Heterogeneity: $J^2 = 0\%$, $\tau^2 = 0$, $\chi_1^2 = 0.35$ ($p = 0.55$)				
Patients with COPD-only (general population)				
Lifelines	294	7.268	4.0 [3.6: 4.5]	+
Danish Twin Registry	85	1.656	5.1 [4.1: 6.3]	
Common effect model		8.924	4.3 [3.9: 4.7]	•
Random effects model		-,	4.5 [3.6: 5.6]	•
Heterogeneity: $J^2 = 74\%$, $\tau^2 = 0.02$, $\chi^2_1 = 3.91$ (<i>p</i> = 0.05)				
Patients with asthma-only (general population)				
Lifelines	23	1.159	2.0 [1.3: 3.0]	Ŧ
Danish Twin Registry	12	408	2.9 [1.5: 5.1]	
Common effect model		1.567	2.3 [1.6: 3.1]	•
Random effects model		,	2.3 [1.6: 3.3]	•
Heterogeneity: $l^2 = 20\%$, $\tau^2 = 0.02$, $\chi_1^2 = 1.25$ ($p = 0.26$)				
Patients with AO (clinic-based)				
COSYCONET	28	371	7.5 [5.1; 10.7]	- <u></u> -
ECLIPSE	44	424	10.4 [7.6; 13.7]	- <u></u> -
Urban Training	0	15	0.0 [0.0; 21.8]	
PAC-COPD	0	22	0.0 [0.0; 15.4]	
Common effect model		832	9.0 [7.2; 11.2]	•
Random effects model			8.7 [6.3; 11.8]	•
Heterogeneity: $I^2 = 17\%$, $\tau^2 = 0.03$, $\chi_3^2 = 3.63$ ($p = 0.30$)				
Patients with COPD-only (clinic-based)				
COSYCONET	162	1,811	8.9 [7.7; 10.4]	
ECLIPSE	139	1,595	8.7 [7.4; 10.2]	⊕
Urban Training	5	351	1.4 [0.5; 3.3]	+
PAC-COPD	31	292	10.6 [7.3; 14.7]	— —
Common effect model		4,049	8.7 [7.9; 9.7]	•
Random effects model			6.4 [2.8; 13.9]	
Heterogeneity: $J^2 = 84\%$, $\tau^2 = 0.71$, $\chi_3^2 = 19.01$ (p < 0.01)				
			_	0 10 20 30 40
			Pre	evalence (%) of myocardial infarction

Figure S3.8. Meta-analyzed (prevalence) of myocardial infarction history.

	Comorbidity	Patients	Proportion (%)	Inverse-variance
	n	n	[95%CI]	method
Patients with $\Delta \Omega$ (general nonulation)				
Rotterdam Study	5	101	5 0 [1 6· 11 2]	_
Lifelines	17	921	1 8 [1 1 2 9]	
Danish Twin Registry	9	258	35[16:65]	
Common effect model	3	1 280	26[18:37]	
Bandom offocts model		1,200	2.0 [1.0, 0.7]	
Heterogeneity: $J^2 = 60\%$, $\tau^2 = 0.16$, $\chi^2_2 = 4.97$ ($p = 0.08$)			2.5 [1.0, 5.2]	•
Patients with COPD-only (general population)				
Rotterdam Study	35	775	4.5 [3.2: 6.2]	-
Lifelines	153	7 261	21[18:25]	+
Danish Twin Registry	86	1 658	52[42:64]	
Common effect model		9 694	31[27:35]	•
Random effects model		0,001	3.6 [2.1: 6.3]	•
Heterogeneity: $J^2 = 96\%$, $\tau^2 = 0.25$, $\chi^2_2 = 52.07$ ($p < 0.01$)			0.0 [2.1., 0.0]	
Patients with asthma-only (general population)				
Rotterdam Study	4	404	1.0 [0.3; 2.5]	-
Lifelines	16	1,148	1.4 [0.8; 2.3]	
Danish Twin Registry	22	409	5.4 [3.4; 8.0]	
Common effect model		1,961	2.7 [2.0; 3.7]	•
Random effects model			2.1 [0.7; 5.7]	
Heterogeneity: $J^2 = 91\%$, $\tau^2 = 0.76$, $\chi^2_2 = 22.01 (p < 0.01)$			• • •	
Patients with AO (clinic-based)				
COSYCONET	14	371	3.8 [2.1; 6.3]	
ECLIPSE	15	433	3.5 [2.0; 5.6]	
Urban Training	0	15	0.0 [0.0; 21.8]	•
PAC-COPD	1	22	4.5 [0.1; 22.8]	•
Common effect model		841	3.6 [2.6; 5.1]	◆
Random effects model			3.6 [2.6; 5.1]	•
Heterogeneity: $J^2 = 0\%$, $\tau^2 = 0$, $\chi_3^2 = 0.12$ ($p = 0.99$)				
Patients with COPD-only (clinic-based)				
COSYCONET	80	1,811	4.4 [3.5; 5.5]	
ECLIPSE	64	1,600	4.0 [3.1; 5.1]	
Urban Training	26	351	7.4 [4.9; 10.7]	
PAC-COPD	11	292	3.8 [1.9; 6.6]	
Common effect model		4,054	4.5 [3.9; 5.2]	•
Random effects model			4.7 [3.6; 6.2]	◆
Heterogeneity: $J^2 = 63\%$, $\tau^2 = 0.06$, $\chi_3^2 = 8.05$ ($p = 0.04$)				
				U 10 20 30 40
				Prevalence (%) of stroke

Figure S3.9. Meta-analyzed (prevalence) of stroke history.

	AO	Asthma-only	COPD-only			
	n (%)	n (%)	n (%)			
DTR (population-based cohort)						
Osteoporosis	27 (10.3)	32 (7.8)	90 (5.4)			
GERD	25 (9.7)	43 (10.5)	107 (6.5)			
U-BIOPRED (clinic-based cohort)						
Osteoporosis	21 (31.3)	61 (28.4)	NA			
GERD	27 (40.3)	104 (48.4)	NA			
CAD	5 (7.5)	9 (4.2)	NA			
Depression	4 (6.0)	19 (8.8)	NA			
Hypertension	25 (37.3)	93 (43.3)	NA			
Diabetes	7 (10.5)	27 (12.6)	NA			

Table S9. Prevalence of comorbidities which could not be meta-analyzed.

CAD = coronary artery disease; DTR = the Danish Twin Registry; GERD = gastro-esophageal reflux disease. Osteoporosis and GERD were not meta-analyzed as only data from DTR was available for population-based cohorts. Comorbidities in asthma-based cohorts were not meta-analyzed as only data from U-BIOPRED was available.

A) Compared to COPD without asthma history







Figure S4. Meta-analysis of comorbidities of LLN-defined AO.

Comparison of asthma with LLN-defined airflow obstruction with COPD-only (A) and asthma-

only (B). Odds ratios were adjusted for age, sex, smoking status, and body mass index.