Phenotyping asthma with airflow obstruction in middle-aged and older adults

Bertels, Xander; Edris, Ahmed; Garcia-Aymerich, Judith; Faner, Rosa; Meteran, Howraman; Sigsgaard, Torben; Alter, Peter; Vogelmeier, Claus; Olvera, Nuria; Kermani, Nazanin Zounemat

Published in:
BMJ open respiratory research

DOI:
10.1136/bmjresp-2023-001760

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 ,[3,4] Rosa Faner,[4,5,6] Howraman Meteran,[7,8] Torben Sigsgaard,[8] Peter Alter,[9] Claus Vogelmeier,[9,10] Nuria Olvera,[4,5] Nazanin Zounemat Kermani,[11] Alvar Agusti,[4,5,12,13] Gavin C Donaldson ,[11] Jadwiga A Wedzicha,[11] Guy G Brusselle,[2,14,15] Helena Backman,[16] Eva Rönmark,[16] Anne Lindberg ,[16] Judith M Vonk,[17,18] Kian Fan Chung,[11] Ian M Adcock ,[11] Maarten van den Berge,[18,19] Lies Lahousse [1,2]

To cite: Bertels X, Edris A, Garcia-Aymerich J, *et al*. Phenotyping asthma with airflow obstruction in middle-aged and older adults: a CADSET clinical research collaboration. *BMJ Open Respir Res* 2023;**10**:e001760. doi:10.1136/bmjresp-2023-001760

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjresp-2023-001760).

Received 12 April 2023
Accepted 31 July 2023

For numbered affiliations see end of article.

Correspondence to
Professor Lies Lahousse; lies.lahousse@ugent.be

ABSTRACT

Background The prevalence and clinical profile of asthma with airflow obstruction (AO) remain uncertain. We aimed to phenotype AO in population- and clinic-based cohorts.

Methods This cross-sectional multicohort study included adults ≥50 years from nine CADSET cohorts with spirometry data (N=69 789). AO was defined as ever diagnosed asthma with pre-BD or post-BD FEV_1/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% CI 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.

Conclusions AO 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.

WHAT IS ALREADY KNOWN ON THIS TOPIC

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

WHAT THIS STUDY ADDS

⇒ AO patients show more clinically relevant dyspnoea compared with both asthma without airflow obstruction and COPD without asthma history. Second, AO 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) AO and concomitant coronary artery disease in clinical practice.

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 (FEV_1/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 ≥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 FEV_1/FVC <0.7 in population-based studies and a postbronchodilator FEV_1/FVC <0.7 in clinic-based cohorts). Asthma-only was defined as ever physician-diagnosis of asthma and FEV_1/FVC ≥0.7. COPD-only was defined as FEV_1/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 <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, asthma-based 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 AO

A total of 69 789 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=63 459), 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 FEV_1% predicted and FEV_1/FVC values of their respective cohort types (online supplemental table S2).

When FEV_1/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 ≥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.

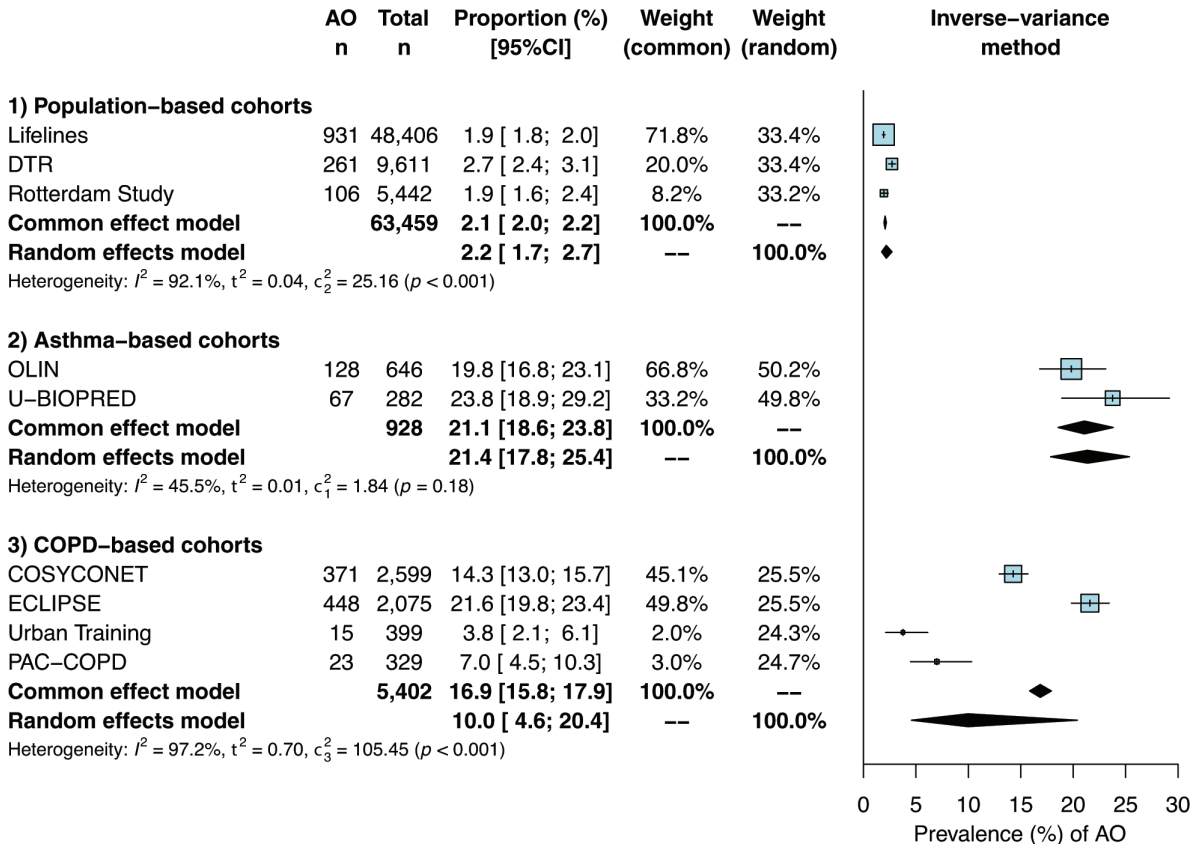

Figure 1 Meta-analysed prevalence of asthma with airflow obstruction (AO) in adults aged 50 years and older in population-based and clinic-based cohorts. COPD, chronic obstructive pulmonary disease. DTR, Danish Twin Registry.

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/µL), 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 FEV_1% 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 asthma-only 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 with asthma-only and COPD-only in population-based and clinic-based cohorts

	Population-based cohorts			Asthma-based cohorts		COPD-based cohorts	
	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% CI)	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% CI)	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% CI)	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% CI)	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% CI)	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% CI)	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% CI)	–	–	–	–	–	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% CI)	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% CI)	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)*	–	–	–	2.2 (3.5)	2.1 (3.8)	3.0 (3.8)	3.7 (5.0)
Serum IgE (ie,/mL), median (IQR)*	–	–	–	120 (292)	110 (221)	78 (192)	54 (116)

*Summary statistics of individual cohorts were meta-analysed, except for CRP and IgE for which only single-study data were available.
AO, asthma with airflow obstruction; BEC, blood eosinophil counts; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; FEV1, forced expiratory volume in 1 second; FEV1/FVC, ratio of FEV1 to FVC; FVC, forced vital capacity; IgE, immunoglobulin E; mMRC, modified Medical Research Council Dyspnoea; WBC, white blood cell count.

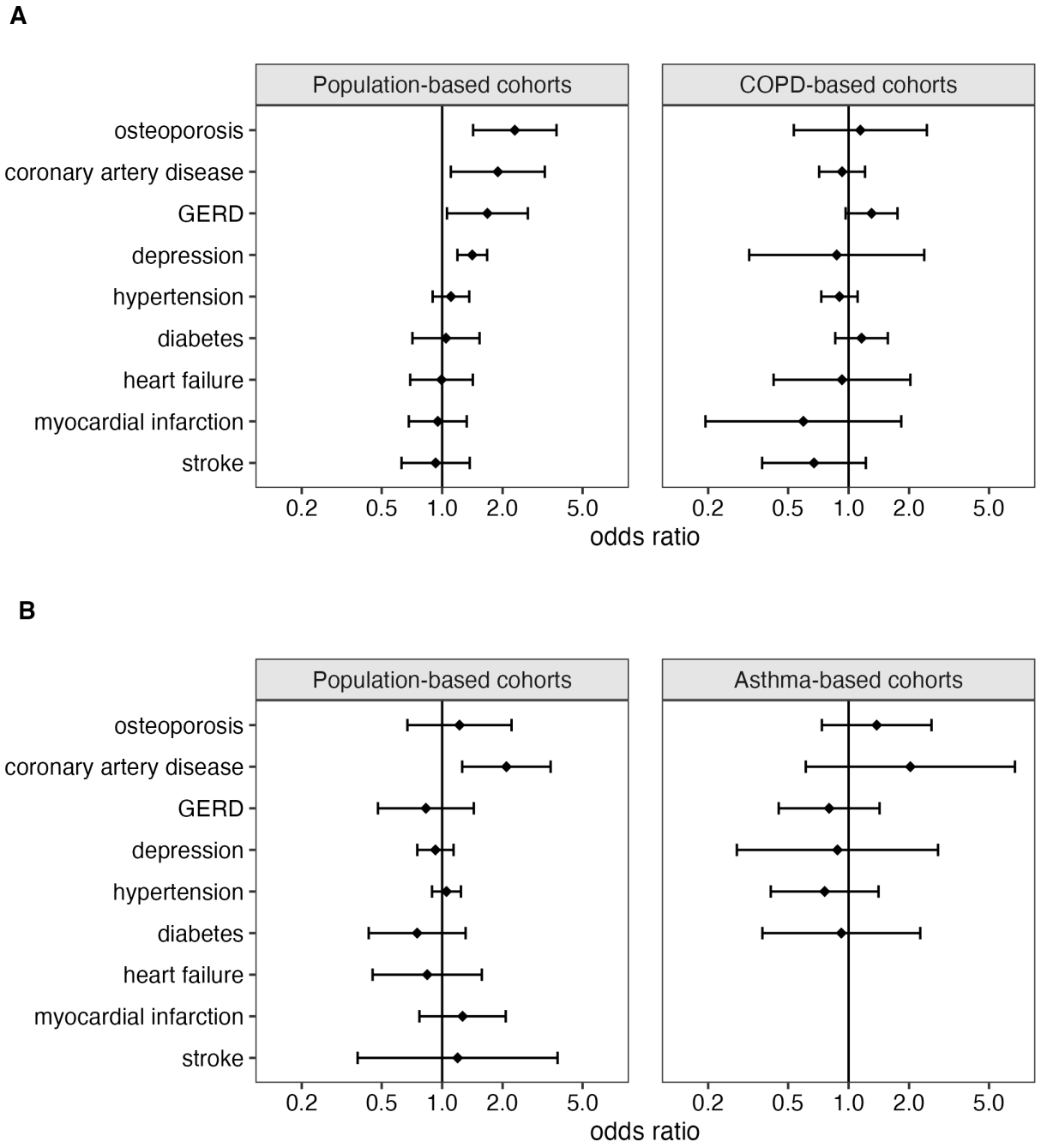

Figure 2 Meta-analysis of comorbidities among patients with asthma with airflow obstruction (AO) compared with COPD without a history of asthma (COPD-only) (A) and compared with asthma without airflow obstruction (asthma-only) **(**B). ORs were adjusted for age, sex, smoking status and body mass index. 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=69 789), we have determined the prevalence of asthma with AO in the general population of adults ≥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 COPD-only.

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 (~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 COPD-only. 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 plugging[38] and/or small airway collapse[39]) and investigate its relationship with lung function trajectories (eg, a lower maximally attained vital capacity at young adulthood and accelerated FEV_1 and/or FVC decline).[40]

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 late-onset asthma and prebronchodilator FEV_1<50% are at the highest risk for CAD among patients with obstructive airway diseases from the general population.[49] In clinic-based 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_1 may partly explain these findings. A previous mendelian randomisation study provided evidence for an inverse relationship between FEV_1 and CAD.[50] FEV_1% 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 depression[51], 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 post-bronchodilator spirometry was performed in population-based cohorts, resulting in possible inclusion of asthma patients with reversible airflow obstruction. The use of (long-acting) bronchodilators as part of standard-of-care 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 COPD-only 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
[1]Department of Bioanalysis, Ghent University, Gent, Belgium
[2]Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands
[3]Non-Communicable Diseases and Environment Programme, ISGlobal, Barcelona, Spain
[4]Centro Investigaciones Biomédicas en Red (CIBERES), Instituto de Salud Carlos III, Madrid, Spain
[5]Institut d'Investigacions Biomédiques August Pi i Sunyer (IDIBAPS), Hospital Clinic de Barcelona, Barcelona, Spain
[6]Department of Biomedical Sciences, University of Barcelona, Barcelona, Spain
[7]Department of Respiratory Medicine, Copenhagen University Hospital-Amager and Hvidovre, Kobenhagen, Denmark
[8]Environment, Occupation and Health, Danish Ramazzini Centre, Department of Public Health, Aarhus University, Aarhus, Denmark
[9]Department of Medicine, Pulmonary and Critical Care Medicine, Philipps University of Marburg, Marburg, Germany
[10]Department of Respiratory and Critical Care Medicine and Ludwig Boltzmann Institute for COPD and Respiratory Epidemiology, Otto Wagner Hospital, Vienna, Austria
[11]National Heart and Lung Institute & Data Science Institute, Imperial College London, London, UK
[12]Department of Medicine, University of Barcelona, Barcelona, Spain
[13]Respiratory Institute, Hospital Clinic de Barcelona, Barcelona, Spain

[14]Department of Respiratory Medicine, Erasmus MC, Rotterdam, The Netherlands
[15]Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium
[16]Department of Public Health and Clinical Medicine, Umeå University, Umea, Sweden
[17]Department of Epidemiology, University Medical Centre Groningen, Groningen, The Netherlands
[18]Groningen Research Institute for Asthma and COPD (GRIAC), University Medical Centre Groningen, Groningen, The Netherlands
[19]Department 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.

Funding CADSET ERS Clinical Research Collaboration has been supported by financial and other contributions from the following consortium partners: European Respiratory Society (ERS), AstraZeneca UK Ltd, Chiesi Farmaceutici, GlaxoSmithKline LLC, Menarini and Sanofi-Genzyme.

Competing interests LL reports consulting fees from AstraZeneca and speaking/lecture fees from Chiesi and IPSA (non-profit) outside the submitted work. CHV reports presentations at symposia and/or served on scientific advisory boards sponsored by Aerogen, AstraZeneca, Boehringer Ingelheim, CSL Behring, Chiesi, GlaxoSmithKline, Grifols, Insmed, Menarini, Novartis, Nuvaira, MedUpdate, Sanofi and Roche outside the submitted work. AA reports grants from GSK, AstraZeneca and Menarini and speaking/lecture fees from GSK, AstraZeneca, Chiesi, Menarini, CIPLA, Zambon, and Sanofi Regeneron outside the submitted work, and is chair of the GOLD board of directors. JAW reports grants from AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, Novartis, Genentech, and 37Clinical, advisory board fees from AstraZeneca, Epiendo, GSK, Gilead, Novartis, Pieris and Pulmatrix, speaker fees from AstraZeneca, GSK, Boehringer, Recipharm and Novartis, and DSMB chair for Virtus outside the submitted work, and is Editor in Chief of AJRCCM. GGB reports fees for advisory boards and/or lectures from AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, Merck Sharp & Dohme, Novartis, and Sanofi Regeneron outside the submitted work. HB reports personal fees from AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline for presentations at scientific meetings outside the submitted work. AL reports speaking/lecture fees from Boehringer-Ingelheim and Novartis, and participation on a advisory board for AstraZeneca, GSK, Novartis, and Boehringer-Ingelheim outside the submitted work. KFC reports advisory board fees from GSK, AstraZeneca, Roche, Novartis, Merck, Nocion, Shionogi and Rickett-Beckinson and has been renumerated for speaking engagements for GSK, AstraZeneca and Merck outside the submitted work. IMA reports investigator-led awards from GSK and Sanofi in addition to travel awards, speakers' fees and advisory board fees from AZ, Chiesi, GSK, Eurodrug, Kineset, Sanofi and Sunovion outside the submitted work. None declared (XB, AE, JG-A, RF, HM, TS, PA, NO, NZK, GCD, ER, JMV and MvdB).

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval All studies were approved by the institutional ethical committees (online supplemental file 1) and informed consent was obtained from all participants. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. The datasets used and generated in this study are not openly available due to data confidentiality. R scripts are available on reasonable request from the corresponding author.

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

REFERENCES

1 Maselli DJ, Hardin M, Christenson SA, *et al*. Clinical approach to the therapy of asthma-COPD overlap. *Chest* 2019;155:168–77.
2 Hosseini M, Almasi-Hashiani A, Sepidarkish M, *et al*. Global prevalence of asthma-COPD overlap (ACO) in the general population: a systematic review and meta-analysis. *Respir Res* 2019;20:229.
3 Buist AS. Similarities and differences between asthma and chronic obstructive pulmonary disease: treatment and early outcomes. *Eur Respir J Suppl* 2003;39:30s–5s.
4 Criner GJ, Celli BR, Brightling CE, *et al*. Benralizumab for the prevention of COPD exacerbations. *N Engl J Med* 2019;381:1023–34.
5 Tashkin DP, Chipps BE, Trudo F, *et al*. Fixed airflow obstruction in asthma: a descriptive study of patient profiles and effect on treatment responses. *J Asthma* 2014;51:603–9.
6 Ghebre MA, Bafadhel M, Desai D, *et al*. "Biological clustering supports both "Dutch" and "British" hypotheses of asthma and chronic obstructive pulmonary disease". *J Allergy Clin Immunol* 2015;135:63–72.
7 Barnes PJ. Asthma-COPD overlap. *Chest* 2016;149:7–8.
8 Yii ACA, Tan GL, Tan KL, *et al*. Fixed Airways obstruction among patients with severe asthma: findings from the Singapore general hospital-severe asthma phenotype study. *BMC Pulm Med* 2014;14:191.
9 Panizza JA, James AL, Ryan G, *et al*. Mortality and airflow obstruction in asthma: a 17-year follow-up study. *Intern Med J* 2006;36:773–80.
10 Tonga KO, King GG, Farah CS, *et al*. Steroid insensitive fixed airflow obstruction is not related to airway inflammation in older non-Smokers with asthma. *Respir Res* 2018;19:176.
11 Wenzel SE, Schwartz LB, Langmack EL, *et al*. Evidence that severe asthma can be divided Pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am J Respir Crit Care Med* 1999;160:1001–8.
12 James AL, Wenzel S. Clinical relevance of airway remodelling in airway diseases. *Eur Respir J* 2007;30:134–55.
13 Guerra S, Martinez FD. Epidemiology of the origins of airflow limitation in asthma. *Proc Am Thorac Soc* 2009;6:707–11.
14 Çolak Y, Afzal S, Nordestgaard BG, *et al*. Young and middle-aged adults with airflow limitation according to lower limit of normal but not fixed ratio have high morbidity and poor survival: a population-based prospective cohort study. *Eur Respir J* 2018;51:1702681.
15 Sorino C, Pedone C, Scichilone N. Fifteen-year mortality of patients with asthma-COPD overlap syndrome. *Eur J Intern Med* 2016;34:72–7.
16 Bonten TN, Kasteleyn MJ, de Mutsert R, *et al*. Defining asthma-COPD overlap syndrome: a population-based study. *Eur Respir J* 2017;49:1602008.
17 Sin DD, Miravitlles M, Mannino DM, *et al*. What is asthma-COPD overlap syndrome? towards a consensus definition from a round table discussion. *Eur Respir J* 2016;48:664–73.
18 Vanfleteren LEGW, Ullman A, Nordenson A, *et al*. Triple therapy (ICS/LABA/LAMA) in COPD: thinking out of the box. *ERJ Open Res* 2019;5:00185-2018.
19 Agusti A, Faner R, Donaldson G, *et al*. Chronic airway diseases early stratification (CADSET): a new ERS clinical research collaboration. *Eur Respir J* 2019;53:1900217.

20 Vestbo J, Anderson W, Coxson HO, *et al*. Evaluation of COPD Longitudinally to identify predictive Surrogate end-points (ECLIPSE). *Eur Respir J* 2008;31:869–73.
21 Garcia-Aymerich J, Gómez FP, Antó JM, *et al*. Phenotypic characterization and course of chronic obstructive pulmonary disease in the PAC-COPD study: design and methods. *Arch Bronconeumol* 2009;45:4–11.
22 Ikram MA, Brusselle G, Ghanbari M, *et al*. Objectives, design and main findings until 2020 from the Rotterdam study. *Eur J Epidemiol* 2020;35:483–517.
23 Scholtens S, Smidt N, Swertz MA, *et al*. Cohort profile: Lifelines, a three-generation cohort study and Biobank. *Int J Epidemiol* 2015;44:1172–80.
24 Arbillaga-Etxarri A, Gimeno-Santos E, Barberan-Garcia A, *et al*. Long-term efficacy and effectiveness of a behavioural and community-based exercise intervention (urban training) to increase physical activity in patients with COPD: a randomised controlled trial. *Eur Respir J* 2018;52:1800063.
25 Skytthe A, Kyvik KO, Holm NV, *et al*. The Danish twin Registry. *Scand J Public Health* 2011;39(7 Suppl):75–8.
26 Karch A, Vogelmeier C, Welte T, *et al*. The German COPD cohort COSYCONET: aims, methods and descriptive analysis of the study population at baseline. *Respir Med* 2016;114:27–37.
27 Backman H, Hedman L, Stridsman C, *et al*. A population-based cohort of adults with asthma: mortality and participation in a long-term follow-up. *Eur Clin Respir J* 2017;4:1334508.
28 Shaw DE, Sousa AR, Fowler SJ, *et al*. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. *Eur Respir J* 2015;46:1308–21.
29 Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical Tutorial. *Evid Based Ment Health* 2019;22:153–60.
30 R: A language and environment for statistical computing [program] 2022. Vienna, Austria,
31 Mekov E, Nuñez A, Sin DD, *et al*. Update on asthma-COPD overlap (ACO): A narrative review. *Int J Chron Obstruct Pulmon Dis* 2021;16:1783–99.
32 Silva GE, Sherrill DL, Guerra S, *et al*. Asthma as a risk factor for COPD in a longitudinal study. *Chest* 2004;126:59–65.
33 Guerriero M, Caminati M, Viegi G, *et al*. Prevalence and features of asthma-chronic obstructive pulmonary disease overlap in northern Italy general population. *J Asthma* 2019;56:27–33.
34 Enright PL, Mc Clelland RL, Newman AB, *et al*. Underdiagnosis and Undertreatment of asthma in the elderly. *Chest* 1999;116:603–13.
35 Parameswaran K, Hildreth AJ, Chadha D, *et al*. Asthma in the elderly: Underperceived, Underdiagnosed and Undertreated; a community survey. *Respir Med* 1998;92:573–7.
36 Smith LJ. The lower limit of normal versus a fixed ratio to assess airflow limitation: will the debate ever end . *Eur Respir J* 2018;51:1800403.
37 Miravitlles M, Soriano JB, Ancochea J, *et al*. Characterisation of the overlap COPD-asthma phenotype. focus on physical activity and health status. *Respir Med* 2013;107:1053–60.
38 Tang M, Elicker BM, Henry T, *et al*. Mucus plugs persist in asthma, and changes in mucus plugs associate with changes in airflow over time. *Am J Respir Crit Care Med* 2022;205:1036–45.
39 Ueda T, Niimi A, Matsumoto H, *et al*. Role of small Airways in asthma: investigation using high-resolution computed tomography. *J Allergy Clin Immunol* 2006;118:1019–25.
40 Agusti A, Faner R. Lung function Trajectories in health and disease. *Lancet Respir Med* 2019;7:358–64.
41 Kole TM, Vanden Berghe E, Kraft M, *et al*. Predictors and associations of the persistent airflow limitation phenotype in asthma: a post-hoc analysis of the ATLANTIS study. *Lancet Respir Med* 2023;11:55–64.
42 Tan WC, Sin DD, Bourbeau J, *et al*. Characteristics of COPD in never-Smokers and ever-Smokers in the general population: results from the Cancold study. *Thorax* 2015;70:822–9.
43 Lamprecht B, McBurnie MA, Vollmer WM, *et al*. COPD in never Smokers: results from the population-based burden of obstructive lung disease study. *Chest* 2011;139:752–63.
44 Tonga KO, Chapman DG, Farah CS, *et al*. Reduced lung elastic recoil and fixed airflow obstruction in asthma. *Respirology* 2020;25:613–9.
45 Rabe KF, Hurst JR, Suissa S. Cardiovascular disease and COPD: dangerous liaisons *Eur Respir Rev* 2018;27:180057.
46 Niccoli G, Cosentino N. Eosinophils: a new player in coronary Atherosclerotic disease. *Hypertens Res* 2012;35:269–71.
47 Ramon MA, Ter Riet G, Carsin A-E, *et al*. The dyspnoea-inactivity vicious circle in COPD: development and external validation of a conceptual model. *Eur Respir J* 2018;52:1800079.
48 Sattelmair J, Pertman J, Ding EL, *et al*. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. *Circulation* 2011;124:789–95.
49 Ingebrigtsen TS, Marott JL, Vestbo J, *et al*. Coronary heart disease and heart failure in asthma, COPD and asthma-COPD overlap. *BMJ Open Respir Res* 2020;7:e000470.
50 Au Yeung SL, Borges MC, Lawlor DA. Association of genetic instrumental variables for lung function on coronary artery disease risk: A 2-sample Mendelian randomization study. *Circ Genom Precis Med* 2018;11:e001952.
51 Currow DC, Chang S, Reddel HK, *et al*. Breathlessness, anxiety, depression, and function-the BAD-F study: A cross-sectional and population prevalence study in adults. *J Pain Symptom Manage* 2020;59:197–205.
52 Neuman A, Gunnbjörnsdottir M, Tunsäter A, *et al*. Dyspnea in relation to symptoms of anxiety and depression: A prospective population study. *Respir Med* 2006;100:1843–9.
53 Zhu Z, Zhu X, Liu C-L, *et al*. Shared Genetics of asthma and mental health disorders: a large-scale genome-wide cross-trait analysis. *Eur Respir J* 2019;54:1901507.
54 Janson C, Malinovschi A, Amaral AFS, *et al*. Bronchodilator reversibility in asthma and COPD: findings from three large population studies. *Eur Respir J* 2019;54:1900561.

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, MD[8]; Peter Alter, MD[9]; Claus F Vogelmeier, MD[9,10]; Nuria Olvera, MSc[6]; Nazanin Zounemat-Kermani, PhD[11]; Alvar Agusti, MD[5,6]; Gavin C. Donaldson, PhD[11]; Jadwiga A. Wedzicha, MD[11]; Guy G. Brusselle, MD[2,13,14]; Helena Backman, PhD[15]; Eva Rönmark, PhD[16]; Anne Lindberg, MD[16]; Judith M. Vonk, PhD[12,18]; Kian Fan Chung, MD[11]; Ian M. Adcock, PhD[11]; Maarten van den Berge, MD[17,18]; Lies Lahousse, PhD[1,2], on behalf of the CADSET European Respiratory Society Clinical Research Collaboration

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

Table of Content

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 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 Reichenhall (Ethikkommission Bayerische Landesärztekammer); Berlin (Ethikkommission Ärztekammer Berlin); Bochum (Ethikkommission Medizinische Fakultät der RUB); Borstel (Ethikkommission Universität Lübeck); Coswig (Ethikkommission TU Dresden); Donaustauf (Ethikkommission Universitätsklinikum Regensburg); Essen (Ethikkommission Medizinische Fakultät 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 Ärztekammer Westfalen-Lippe); Solingen (Ethikkommission Universität Witten-Herdecke); Ulm (Ethikkommission Universität Ulm); Würzburg (Ethikkommission Universität Würzburg). The study was performed in accordance with the declaration of Helsinki, and all participants gave their written informed 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 FEV_1 of <80% pred and FEV_1/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 FEV_1 of >85% pred and FEV_1/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 FEV_1/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: 19/06/2002 • 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 Clínic 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
Type of study:	asthma-based cohort
Number of sites:	single-center
Population:	2,055 asthma adults from Northern Sweden recruited by postal questionnaire since 1986
Inclusion Criteria:	- Self-reported asthma - Highly suspected asthma
Exclusion Criteria:	No prespecified exclusion criteria.
Ethics committee	Regional Ethical Review Board at Umeå 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 asthmatics, - Smokers and ex-smokers with severe asthma, - Mild/moderate non-smoking asthmatics, - Healthy non-smoking controls
Exclusion Criteria:	No prespecified exclusion criteria.
Ethics committee	Approved by the ethics committee for each participating clinical institution (ClinicalTrials.gov identifier: NCT01982162)

Study:	Rotterdam Study
Type of study:	population-based cohort
Number of sites:	single-center
Population:	14,926 participants
Inclusion Criteria:	Inhabitants of the Ommoord district, Rotterdam, Netherlands, aged 45 years or over.
Exclusion Criteria:	No prespecified exclusion criteria.
Ethics committee	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)

Study:	LifeLines
Type of study:	population-based cohort
Number of sites:	multi-center
Population:	167,729 participants
Inclusion Criteria:	All inhabitants in the Netherlands between 25-50 years of age at recruitment, registered with a GP, and their relatives (parents, partners, children).
Exclusion Criteria:	- Severe psychiatric or physical illness, limited life expectancy (<5 years) - Insufficient knowledge of the Dutch language to complete a Dutch questionnaire.
Ethics committee	Ethics Committee of University Medical Center Groningen (The Netherlands)

Study:	Danish Twin Registry
Type of study:	population-based cohort
Number of sites:	nationwide registry
Population:	136,684 twin pairs (in addition: 775 triplets and 22 quadruplets)
Inclusion Criteria:	Twin cohorts in Denmark including twin pairs born between 1870-2006.
Exclusion Criteria:	No prespecified exclusion criteria.
Ethics committee	The Regional Committees on Health Research Ethics for Southern Denmark (De Videnskabsetiske Komitéer for Region Syddanmark); Journal number S-VF-19980072.

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 ≥ 18.5 and < 25, overweight = BMI ≥ 25 and < 30, obese = BMI ≥ 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 ≥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.

Asthma

- **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 (FEV_1) >12% predicted or 200 mL following inhalation of 400 µg salbutamol), airway hyperresponsiveness (methacholine provocative concentration causing a 20% fall in FEV_1 <8 mg·mL−1, or diurnal peak expiratory flow amplitude >8% of mean), or a decrease in FEV_1 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

Stroke

- **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

Osteoporosis

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

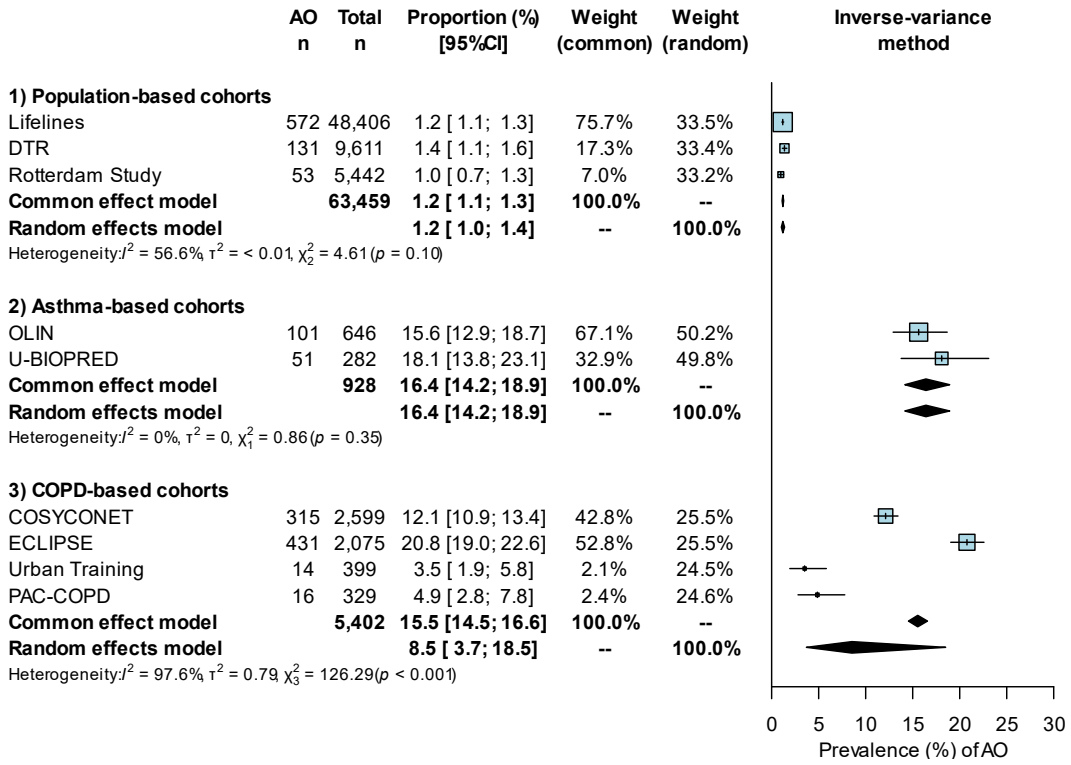

Figure S1. Meta-analyzed prevalence of asthma with LLN-defined airflow obstruction.

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

	AO n (%)	FEV_1% pred mean (95%CI)	FVC% pred mean (95%CI)	FEV_1/FVC % mean (95%CI)
Population cohorts				
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 S3. Sample sizes and p-values accompanying Table 1 in the manuscript.

	Population cohorts			**Asthma cohorts**		**COPD 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							
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
Overweight *P*-value	REF	0.902	0.556	REF	0.898	REF	0.929
Obese *P*-value	REF	**<0.001**	**0.001**	REF	**<0.001**	REF	0.932
Smoking status							
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 disease history							
N	931	1161	7296	195	733	393	2104
P-value	REF	0.644	**<0.001**	REF	0.588	REF	0.365
Chronic bronchitis							
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 (%) predicted							
N	1197	1840	8627	195	730	857	4088
P-value	REF	**<0.001**	**<0.001**	REF	**<0.001**	REF	0.675
FVC (%) predicted							
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 blood WBC (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 300 cells/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 (IE/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 FEV_1/FVC<0.70) 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 ≥ 18.5 and < 25, overweight = BMI ≥ 25 and < 30, obese = BMI ≥ 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, 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.

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

	Population-based cohorts			Asthma-based cohorts		COPD-based cohorts	
	AO	**Asthma-only**	**COPD-only**	**AO**	**Asthma-only**	**AO**	**COPD-only**
Characteristics							
Age (years), mean (95% CI)	62.7 (58.7-66.7)	63.2 (57.3-69.2)	63.6 (57.8-69.4)	60.3 (57.6-63.0)	59.1 (56.9-61.4)	64.7 (62.9-66.6)	**66.8 (64.5-69.1)**
Female, prop (95% CI)	60.4 (52.4-68.4)	60.8 (54.6-66.9)	51.5 (45.3-57.8)	48.0 (40.1-55.9)	**58.2 (54.7-61.6)**	30.7 (8.1-53.3)	**22.9 (9.0-36.7)**
BMI (kg/m^2), mean (95% CI)	26.5 (26.2-26.8)	27.6 (25.9-29.3)	**25.9 (25.6-26.2)**	26.2 (23.7-28.8)	**28.2 (26.1-30.3)**	27.4 (25.6-29.2)	27.2 (26.2-28.2)
Underweight, prop (95% CI)	0.9 (0.2-1.6)	0.3 (0.0-0.7)	1.6 (0.1-3.1)	0.7 (0.0-2.3)	1.1 (0.0-2.6)	3.6 (1.4-5.8)	2.9 (1.1-4.7)
Normal weight, prop (95% CI)	38.1 (29.5-46.7)	32.2 (21.2-43.1)	42.1 (36.8-47.5)	47.0 (24.9-69.2)	**27.6 (21.7-33.6)**	30.5 (15.2-45.8)	31.1 (22.6-39.7)
Overweight, prop (95% CI)	42.9 (33.1-52.6)	42.9 (40.2-45.6)	42.0 (35.0-49.0)	36.3 (28.5-44.1)	41.2 (31.4-51.1)	36.8 (33.5-40.2)	37.2 (35.5-38.9)
Obese, prop (95% CI)	17.1 (14.4-19.7)	25.0 (11.2-38.7)	**13.5 (12.3-14.6)**	15.6 (0.0-37.3)	**30.3 (13.0-47.7)**	22.4 (17.3-27.4)	27.4 (19.5-35.3)
Never smoker, prop (95% CI)	26.7 (17.6-35.8)	31.1 (20.4-41.9)	**15.2 (9.3-21.2)**	11.5 (4.6-18.3)	25.1 (0.0-58.2)	6.3 (0.0-14.8)	1.5 (0.0-3.3)
Former smoker, prop (95% CI)	51.7 (48.2-55.3)	52.9 (47.0-58.9)	45.7 (35.5-55.9)	34.8 (13.2-56.4)	36.8 (33.4-40.2)	65.4 (62.0-68.7)	68.5 (64.7-72.3)
Current smoker, prop (95% CI)	22.8 (11.7-34.0)	15.7 (3.6-27.9)	**39.1 (25.6-52.6)**	53.8 (25.4-82.2)	**38.6 (2.5-74.7)**	23.5 (5.4-41.6)	29.9 (24.6-35.1)
Pack-years, mean (95% CI)	23.1 (16.6-29.6)	19.7 (13.0-26.3)	**29.9 (25.6-34.2)**	13.9 (7.9-20.0)	18.3 (14.4-22.2)	46.3 (34.0-58.5)	**57.1 (47.5-66.8)**
mMRC score ≥2, prop (95% CI)	41.9 (34.7-49.1)	**25.2 (4.4-46.0)**	**22.1 (5.3-39.0)**	60.4 (50.9-69.9)	**39.8 (35.7-43.9)**	63.2 (36.0-90.4)	59.9 (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 (11.5-44.6)	**13.9 (10.1-17.7)**	16.7 (14.1-19.3)	30.6 (0.0-63.7)	24.0 (0.7-47.3)	54.4 (30.2-78.5)	53.4 (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 (58.1-76.8)	**88.7 (81.5-95.9)**	**71.8 (61.7-82.0)**	53.0 (41.7-64.2)	**78.9 (63.4-94.5)**	49.6 (43.0-56.3)	49.3 (45.4-53.2)
FVC (%) predicted, mean (95% CI)	90.1 (79.7-100.6)	**97.6 (90.8-104.4)**	**94.1 (84.1-104.2)**	77.2 (73.7-80.8)	**88.7 (83.2-94.1)**	77.6 (72.4-82.8)	76.9 (73.9-79.8)
FEV_1/FVC (%), mean (95% CI)	57.6 (54.1-61.0)	**70.6 (61.4-79.8)**	58.2 (55.0-61.4)	53.0 (38.7-67.3)	**71.7 (56.3-87.1)**	49.3 (44.5-54.1)	48.7 (44.7-52.8)
Biomarkers							
Peripheral blood WBC (10^9 cells/L), mean (95% CI)	6.7 (5.8-7.7)	6.7 (5.8-7.7)	7.3 (5.3-9.3)	8.3 (7.6-9.0)	7.7 (7.3-8.0)	7.9 (7.7-8.1)	7.7 (7.3-8.2)
BEC above 300 cells/μL, prop (95% CI)	28.2 (24.4-31.9)	**16.0 (14.0-18.1)**	**16.0 (14.7-17.3)**	52.9 (39.2-66.6)	**35.3 (29.0-41.5)**	23.7 (19.7-27.7)	18.8 (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 FEV_1/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 ≥ 18.5 and < 25, overweight = BMI ≥ 25 and < 30, obese = BMI ≥ 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.

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

	FR-based obstruction		LLN-based obstruction	
	Normal (n = 4132)	**AO (n = 106)**	**Normal (n = 4613)**	**AO (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/m^2), 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)**

AO = asthma with airflow obstruction; FR = fixed ratio (FEV_1/FVC < 0.7); LLN = lower limit of normal (FEV_1/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 obstruction**		**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 obstruction**		**LLN-based obstruction**	
	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-based obstruction**			**LLN-based obstruction**		
	AO n (%)	COPD-only n (%)	P-value	AO n (%)	COPD-only n (%)	P-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.

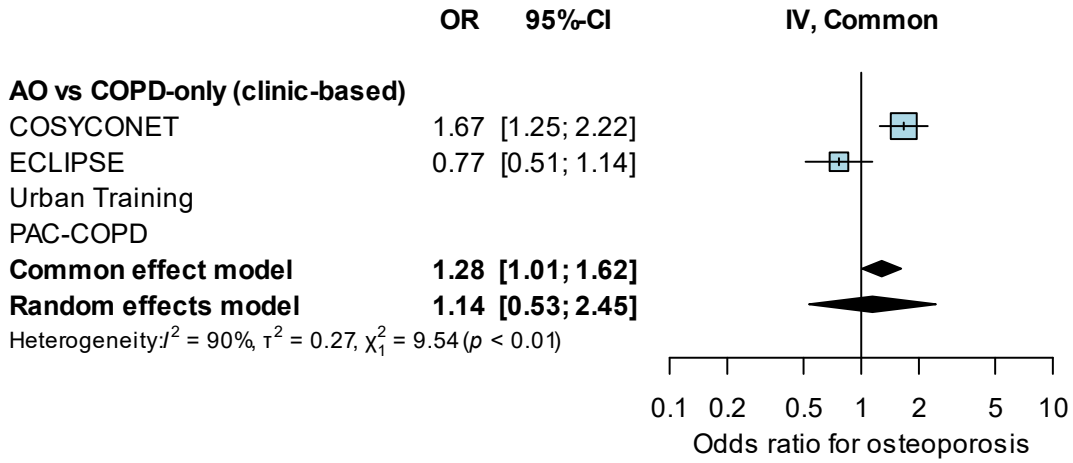

Figure S2.1. Meta-analyzed (adjusted odds) of osteoporosis.

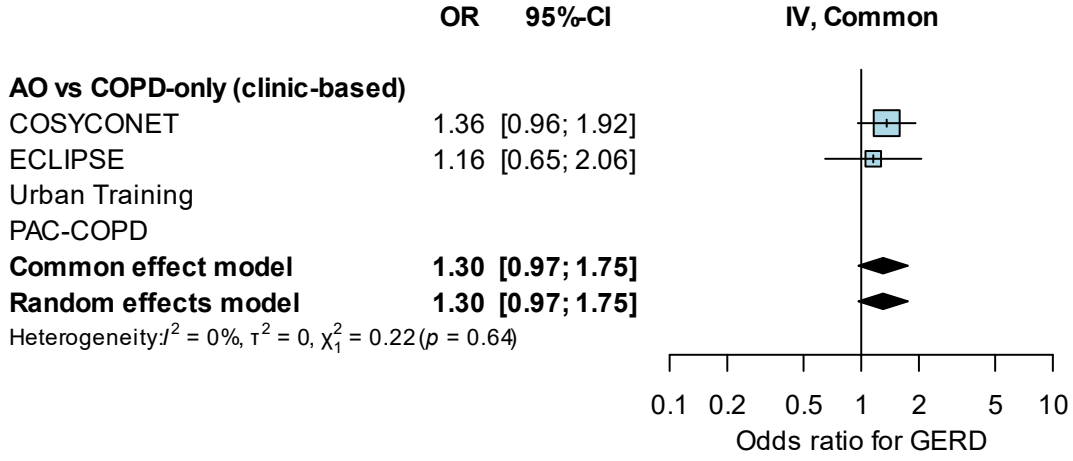

Figure S2.2. Meta-analyzed (adjusted odds) of gastro-esophageal reflux disease.

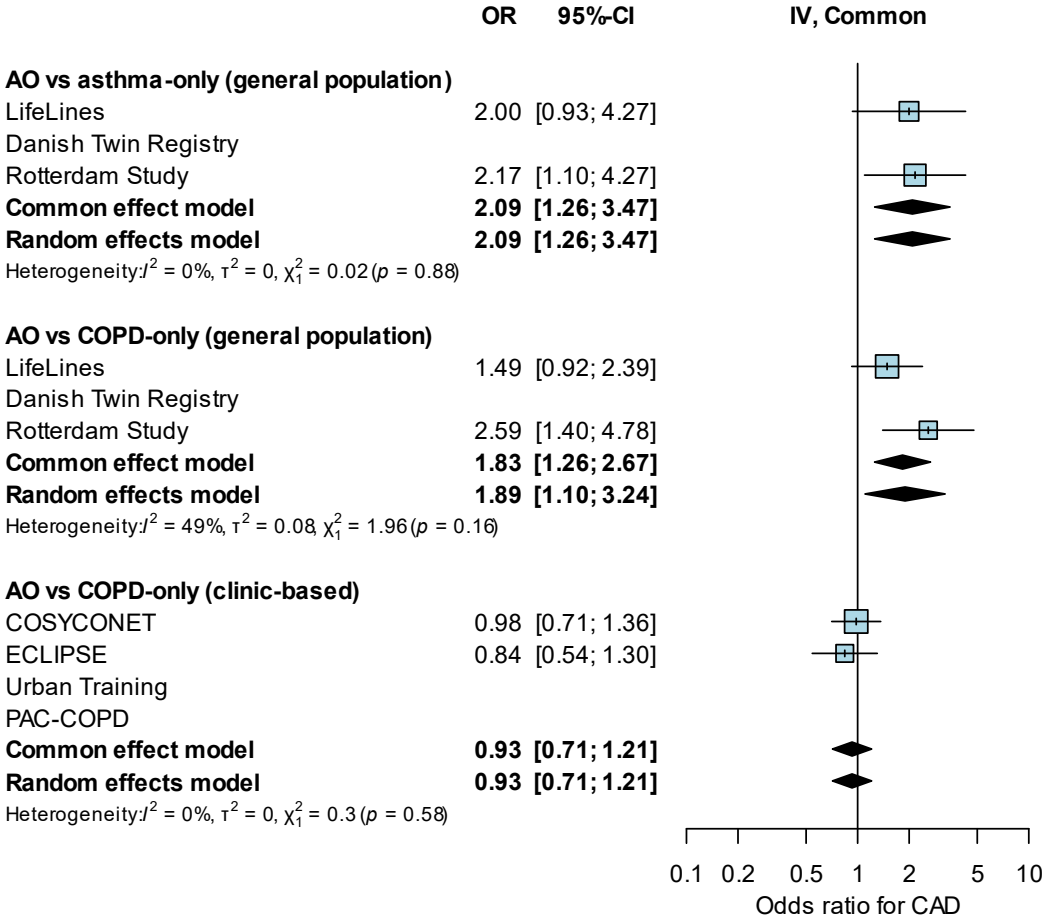

Figure S2.3. Meta-analyzed (adjusted odds) of coronary artery disease.

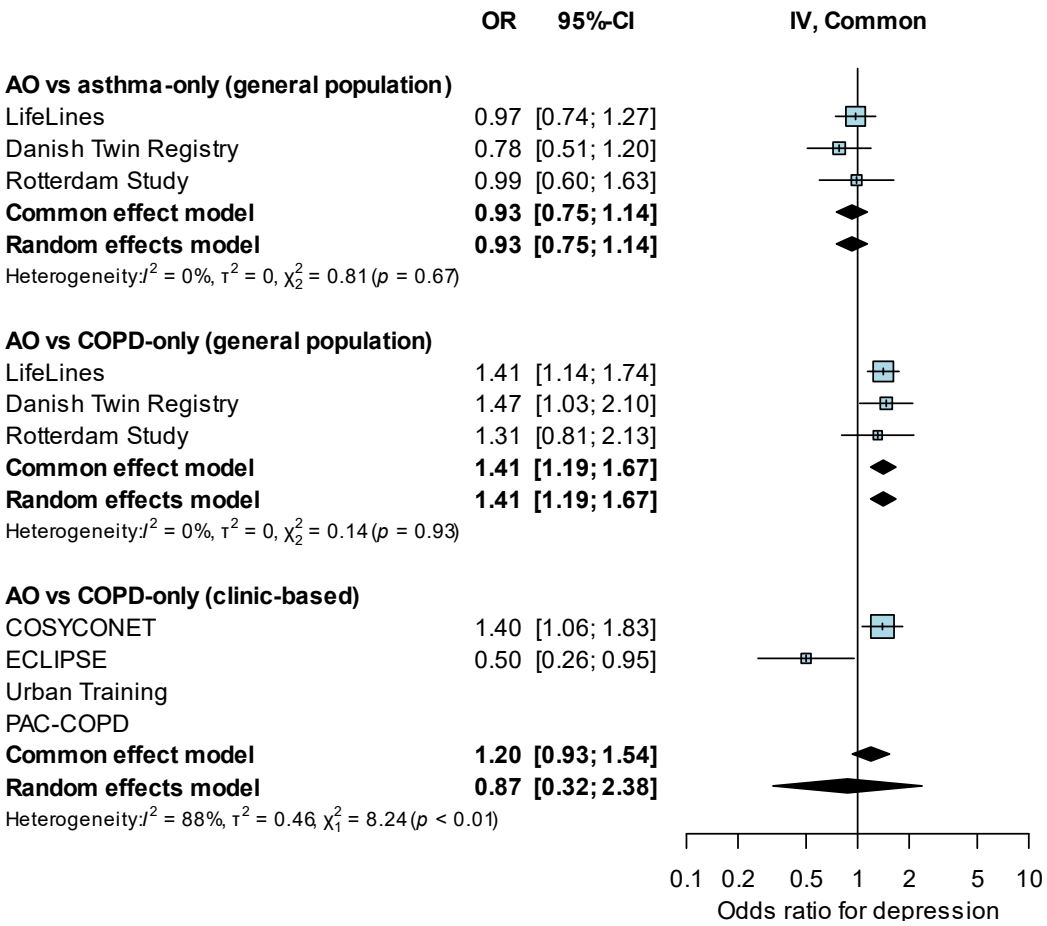

Figure S2.4. Meta-analyzed (adjusted odds) of depression.

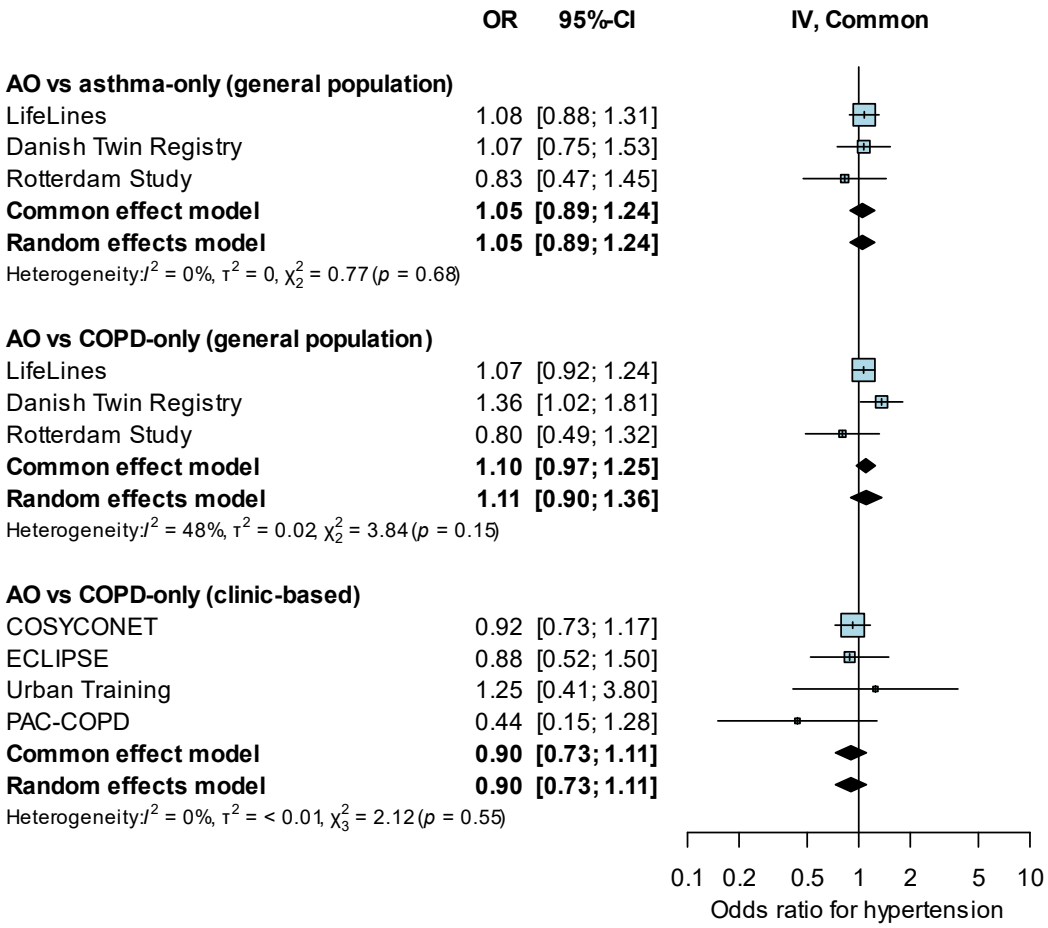

Figure S2.5. Meta-analyzed (adjusted odds) of hypertension.

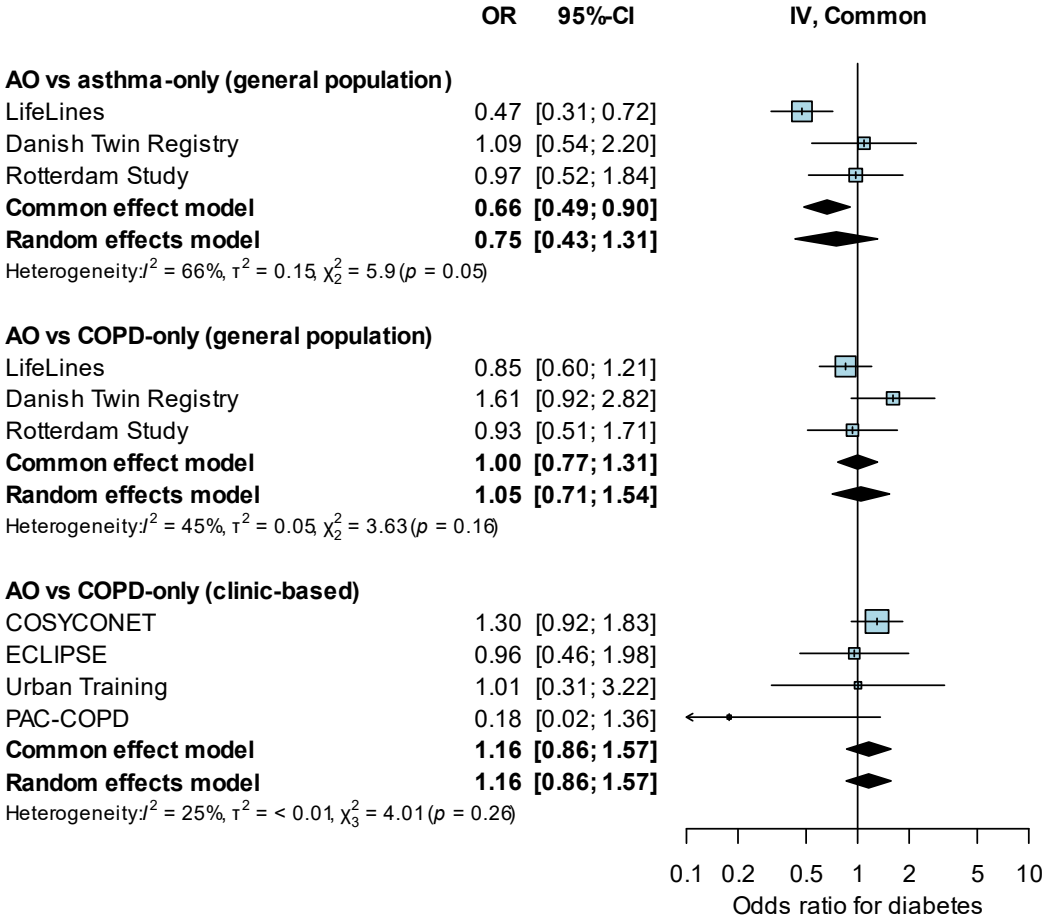

Figure S2.6. Meta-analyzed (adjusted odds) of diabetes mellitus type 2.

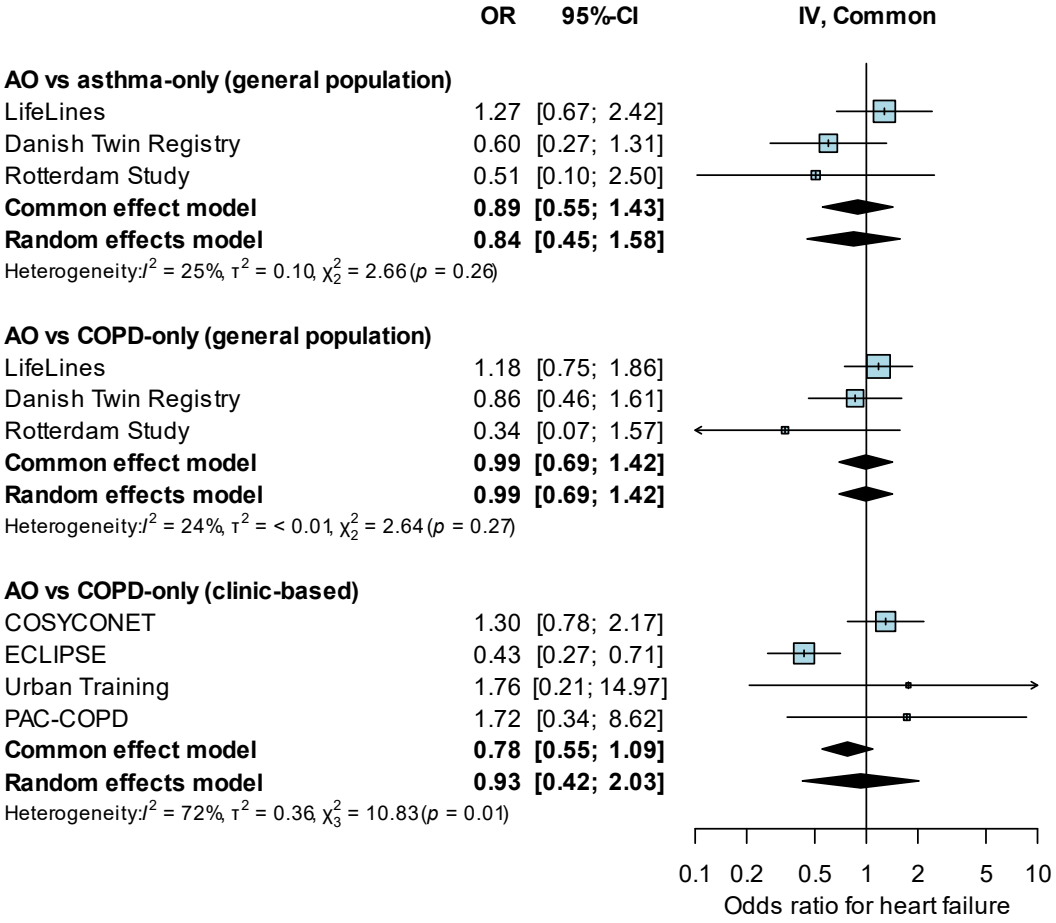

Figure S2.7. Meta-analyzed (adjusted odds) of heart failure.

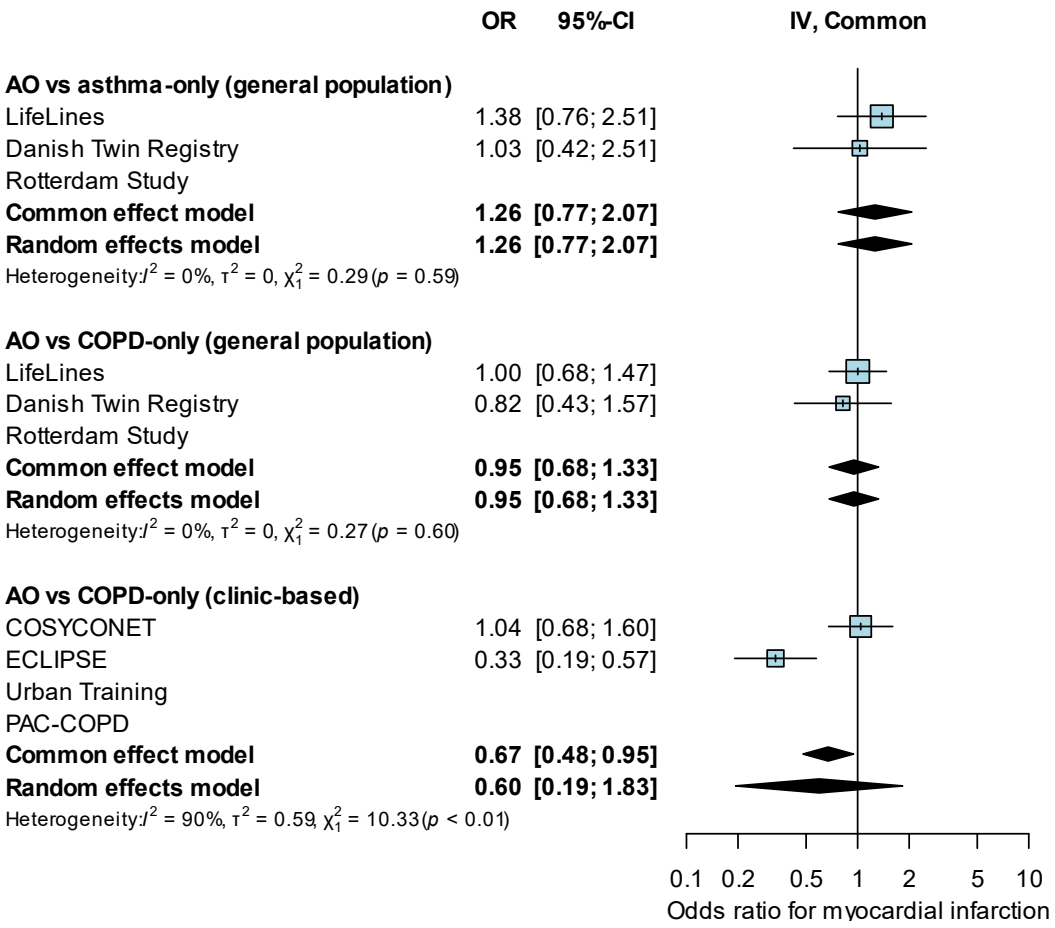

Figure S2.8. Meta-analyzed (adjusted odds) of myocardial infarction history.

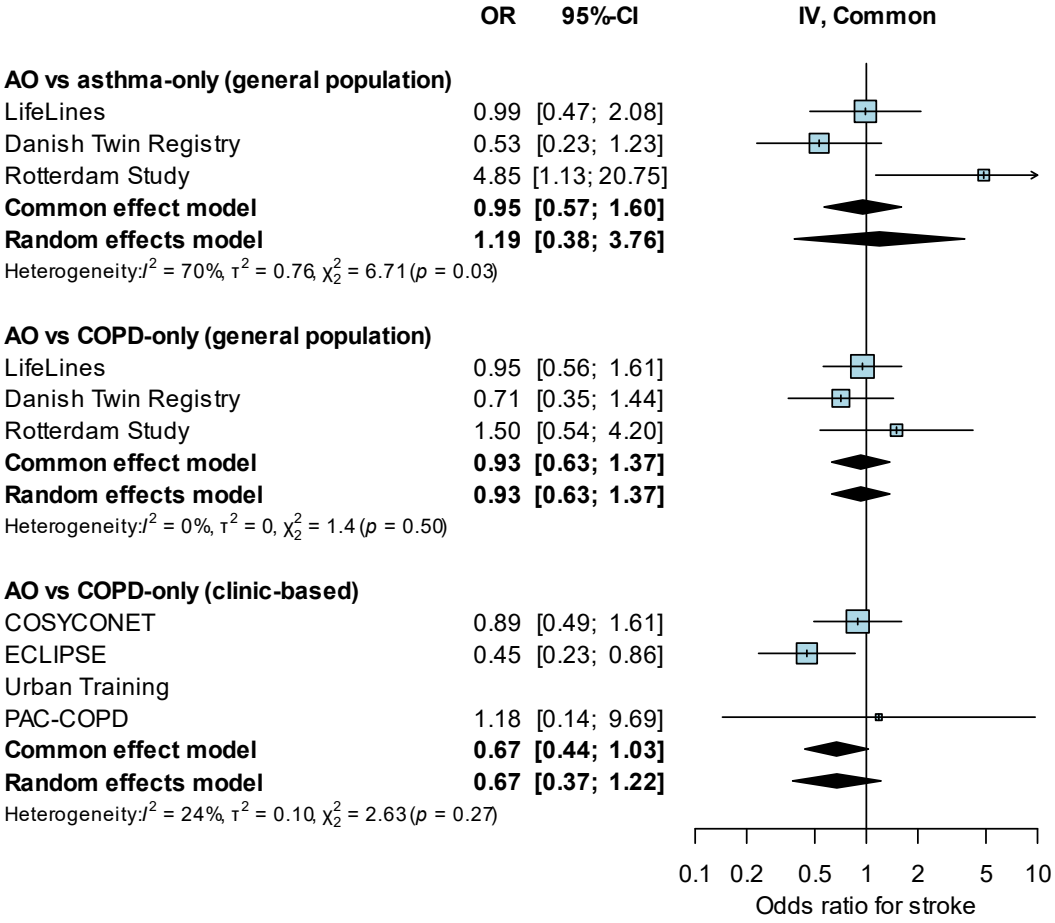

Figure S2.9. Meta-analyzed (adjusted odds) of stroke history.

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

	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 (clinic-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

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 OR (95% CI)	AO vs COPD-only 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)

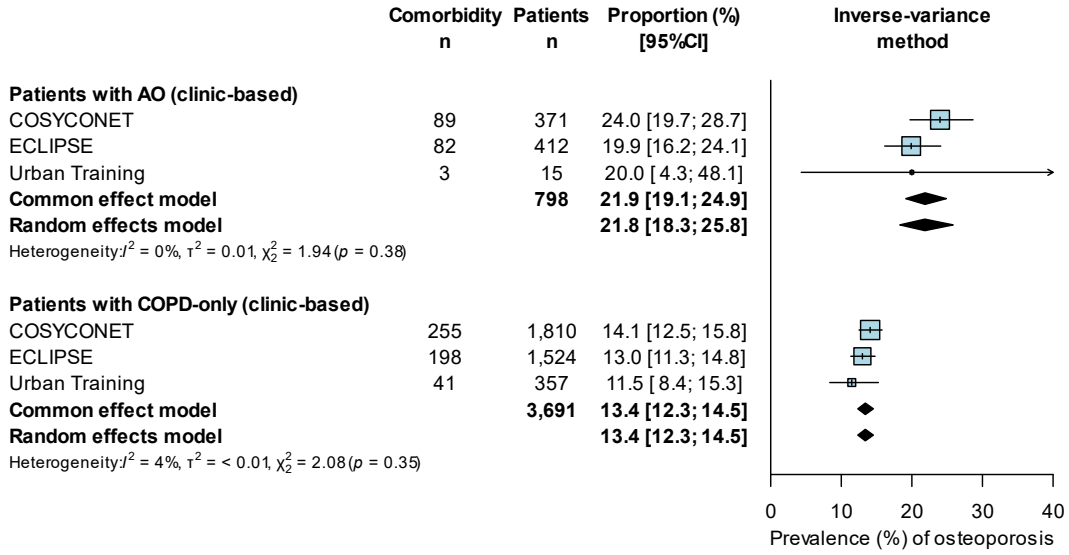

Figure S3.1. Meta-analyzed (prevalence) of osteoporosis.

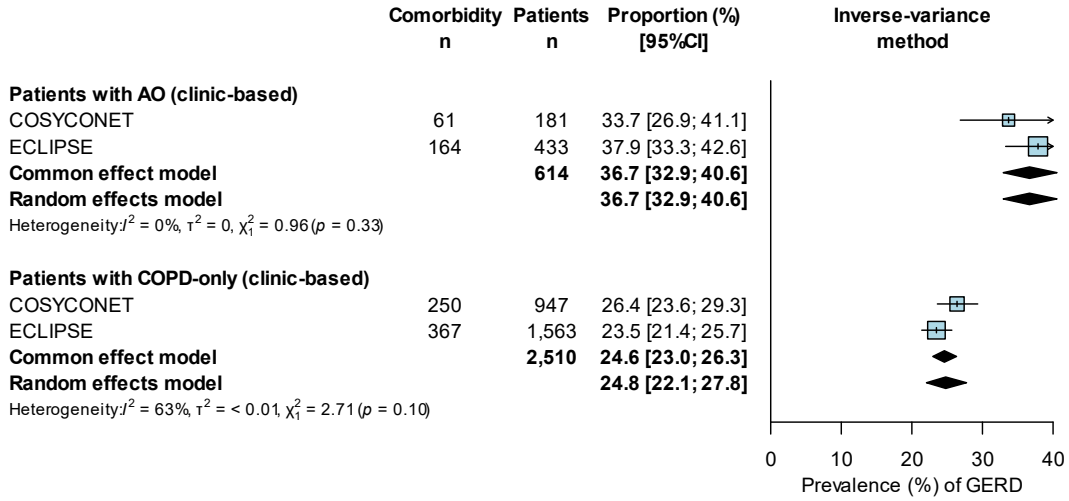

Figure S3.2. Meta-analyzed (prevalence) of gastro-esophageal reflux disease.

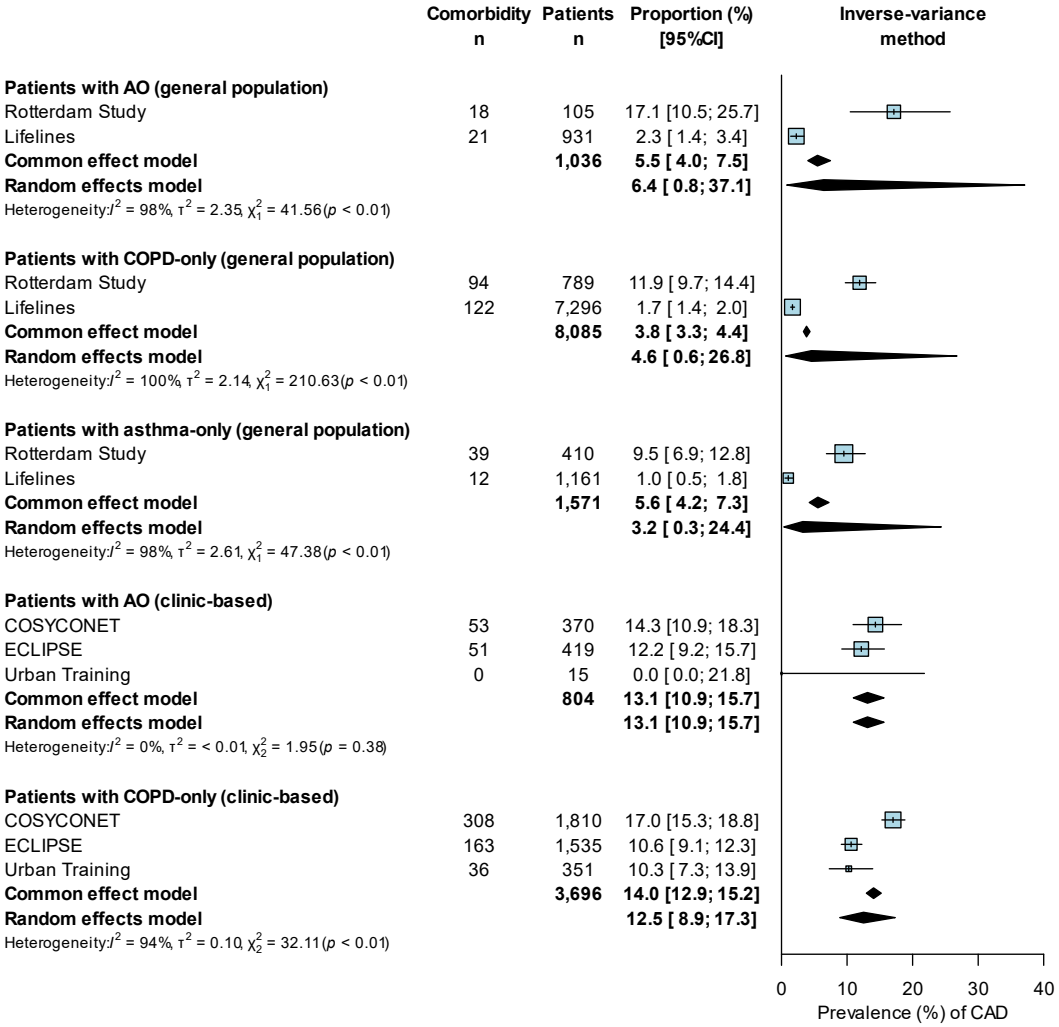

Figure S3.3. Meta-analyzed (prevalence) of coronary artery disease.

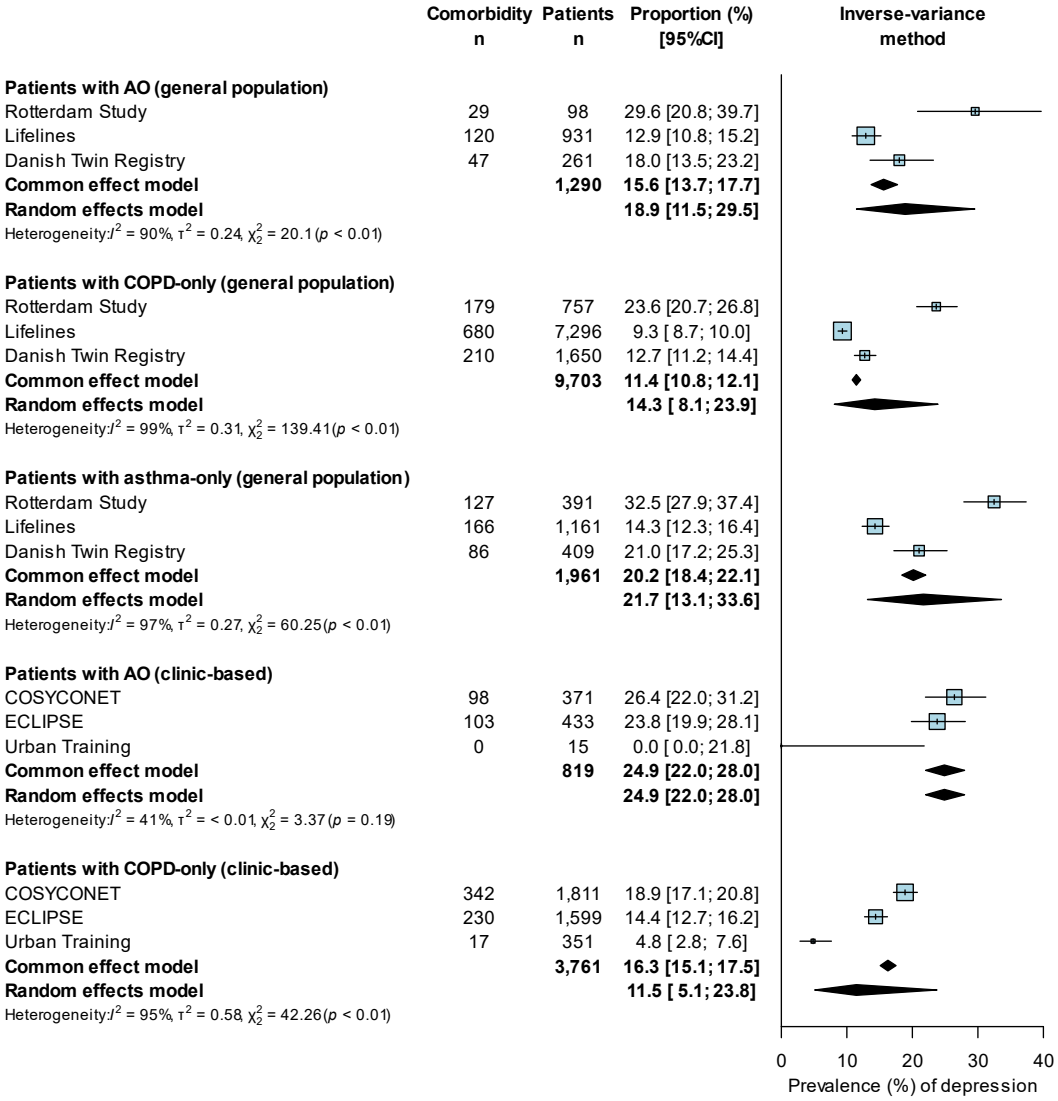

Figure S3.4. Meta-analyzed (prevalence) of depression.

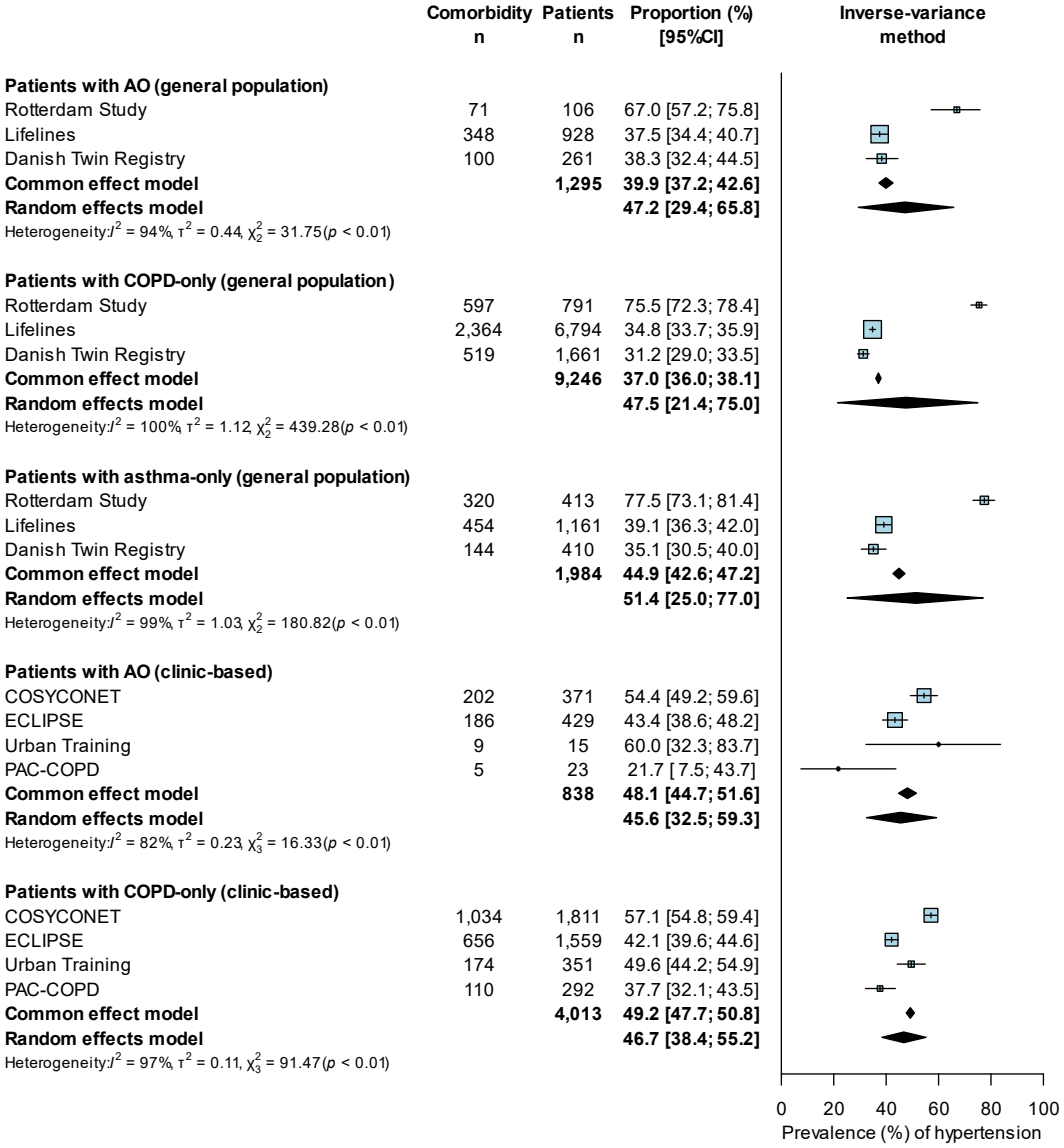

Figure S3.5. Meta-analyzed (prevalence) of hypertension.

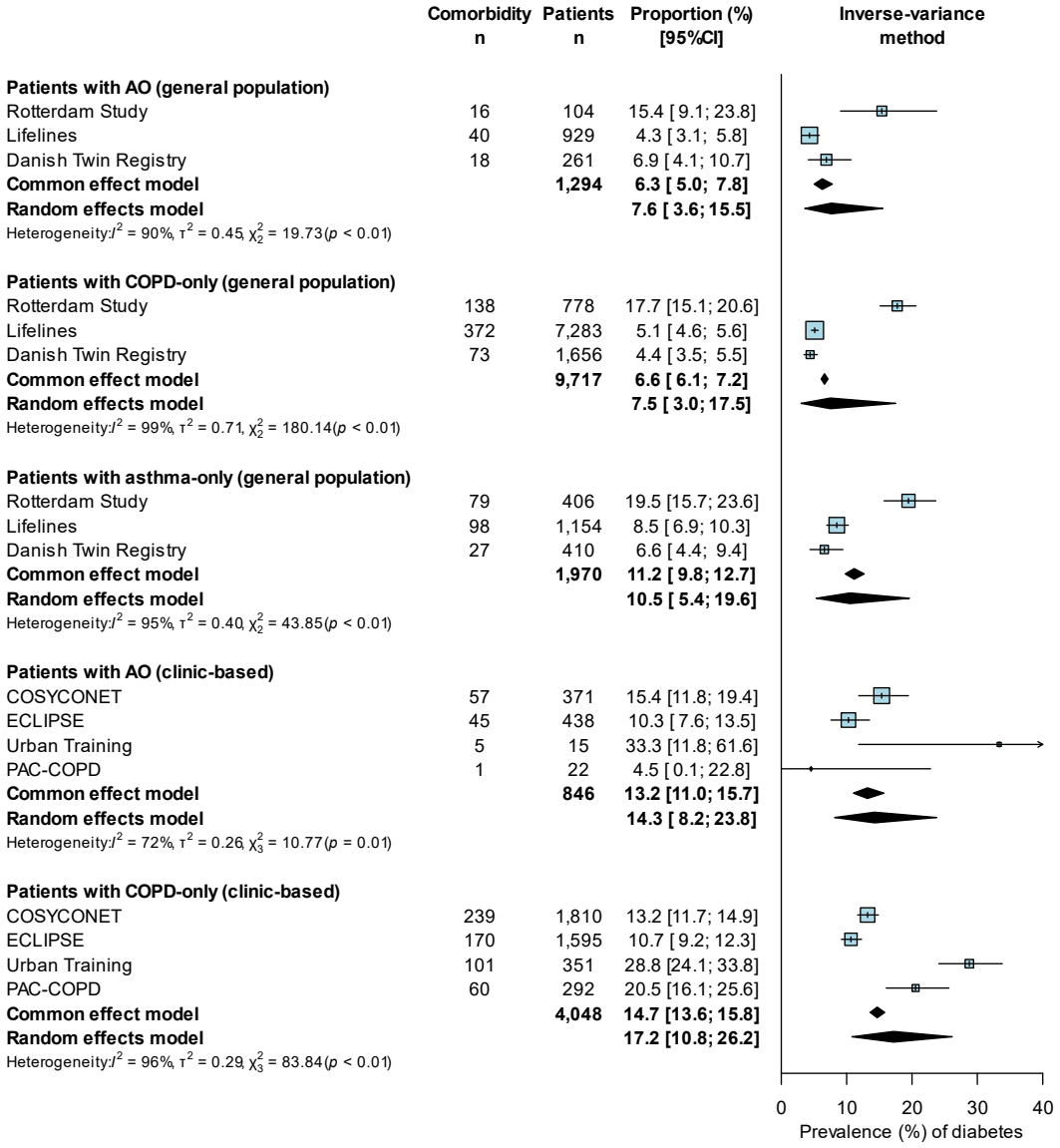

Figure S3.6. Meta-analyzed (prevalence) of diabetes mellitus type 2.

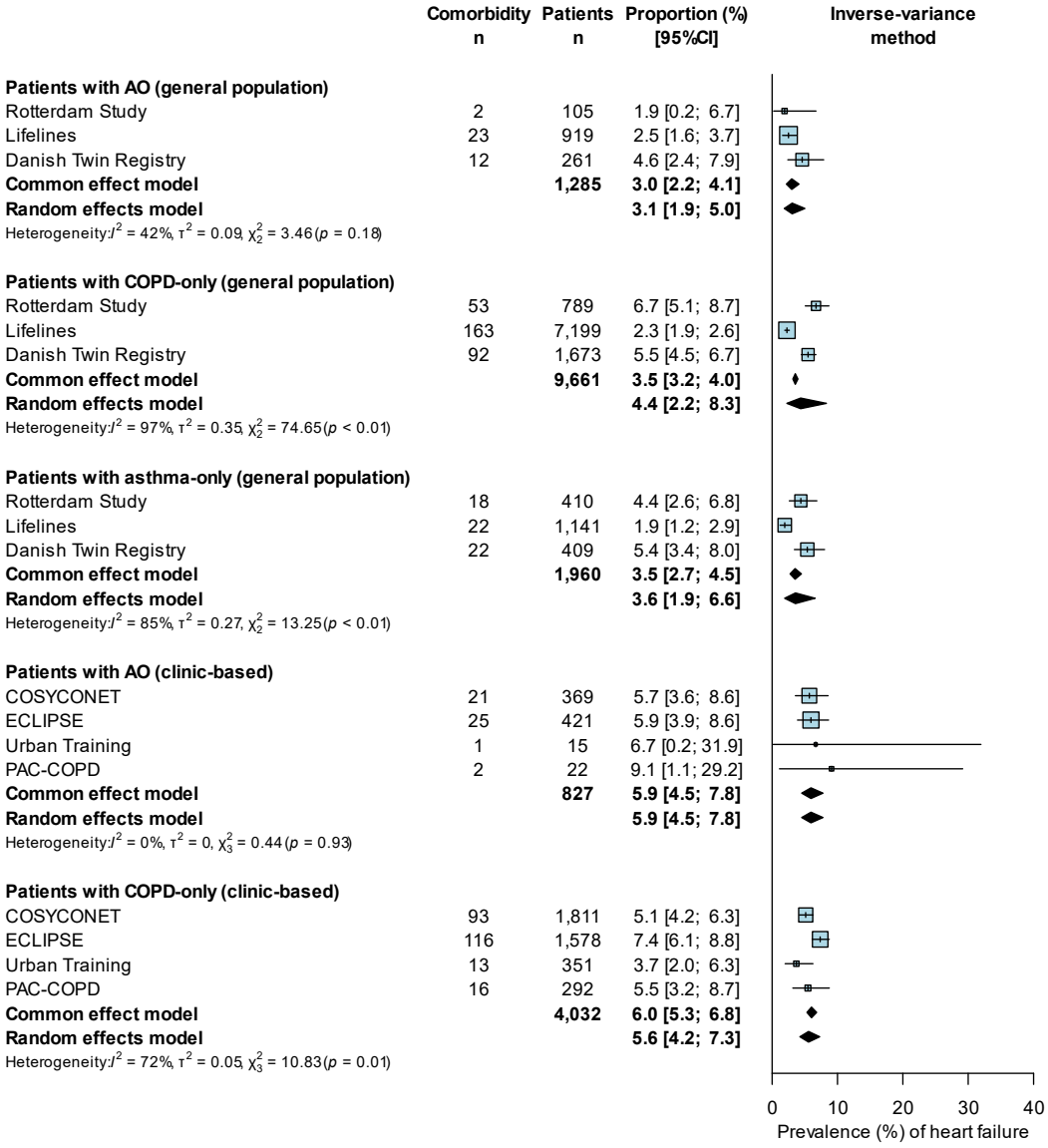

Figure S3.7. Meta-analyzed (prevalence) of heart failure.

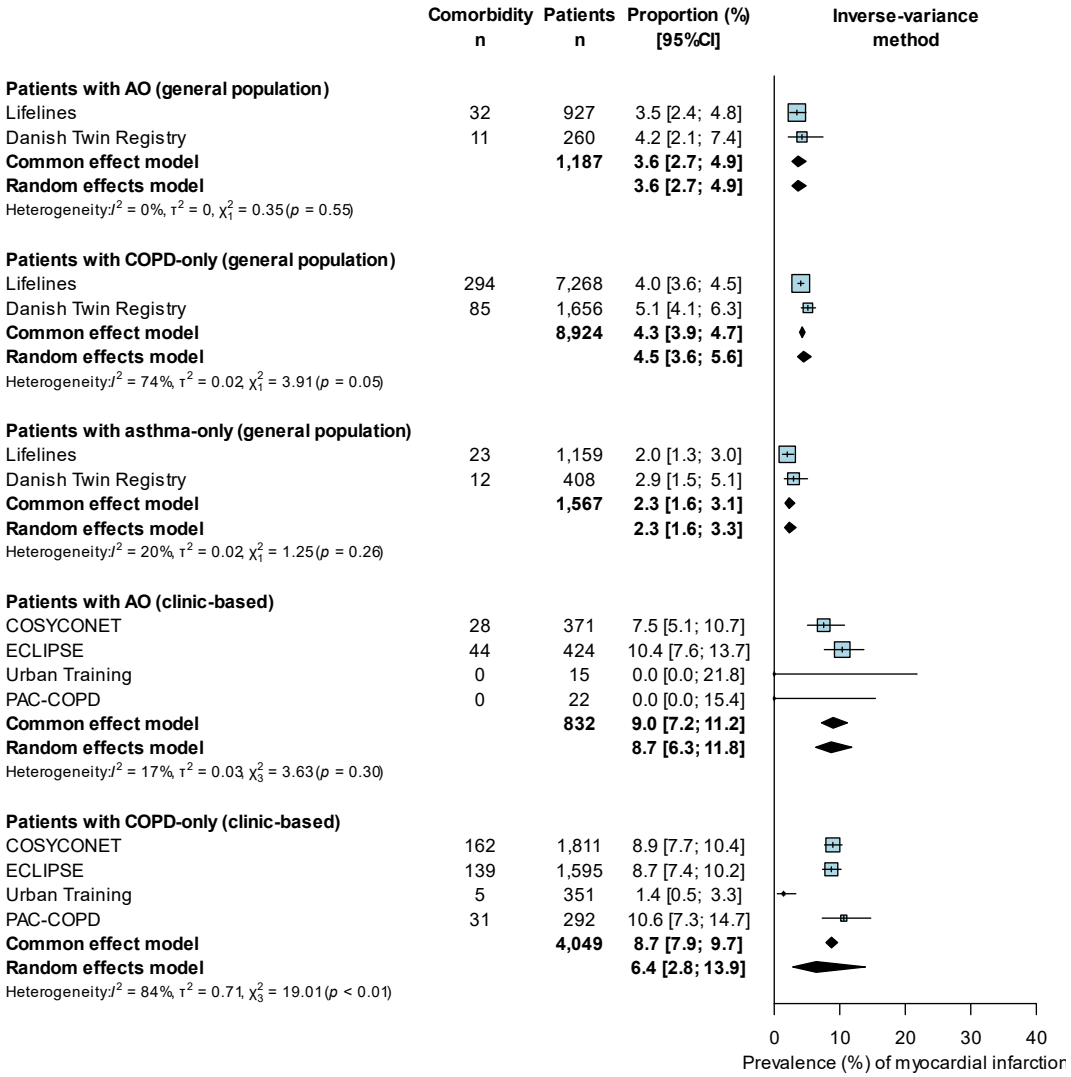

Figure S3.8. Meta-analyzed (prevalence) of myocardial infarction history.

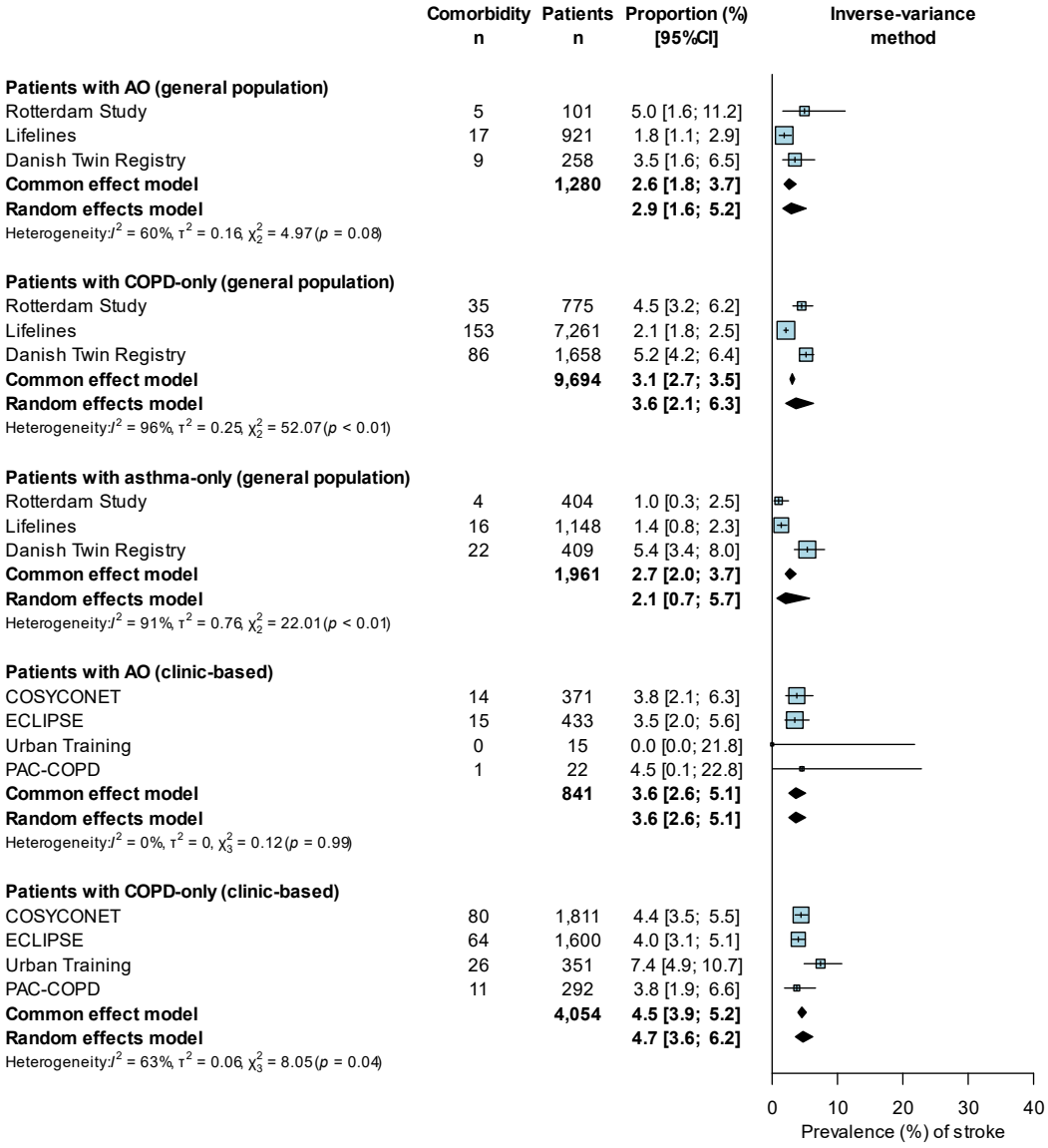

Figure S3.9. Meta-analyzed (prevalence) of stroke history.

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

	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

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.

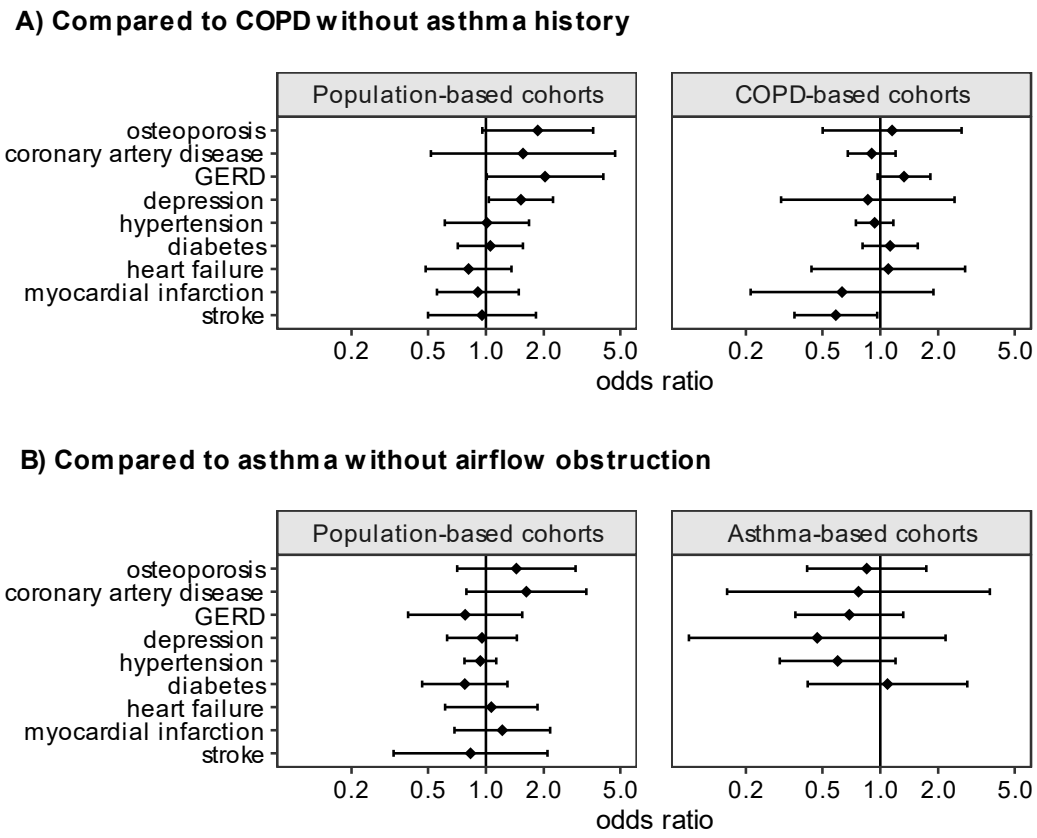

Figure S4. Meta-analysis of comorbidities of LLN-defined AO.

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.