

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

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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 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% 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.

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.

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.

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 airflow 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 $FEV_1/FVC \geq 0.7$. 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.

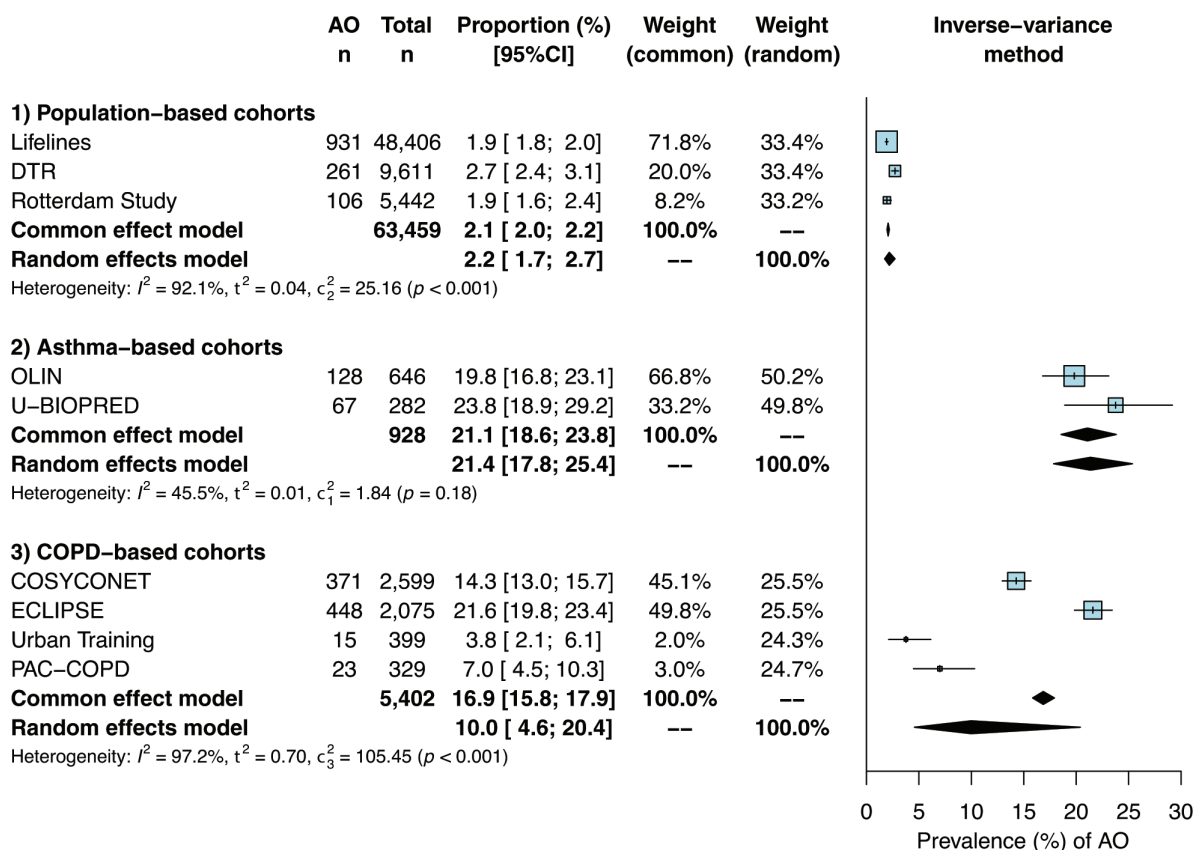


Figure 1 Meta-analysed prevalence of asthma with airflow obstruction (AO) in adults aged 50 years and older in population-based and clinic-based cohorts. COPD, chronic obstructive pulmonary disease. DTR, Danish Twin Registry.

Compared with asthma-only, AO patients were more frequently men, current smokers, had a lower FEV₁% 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 ($\beta = 0.09$ (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.

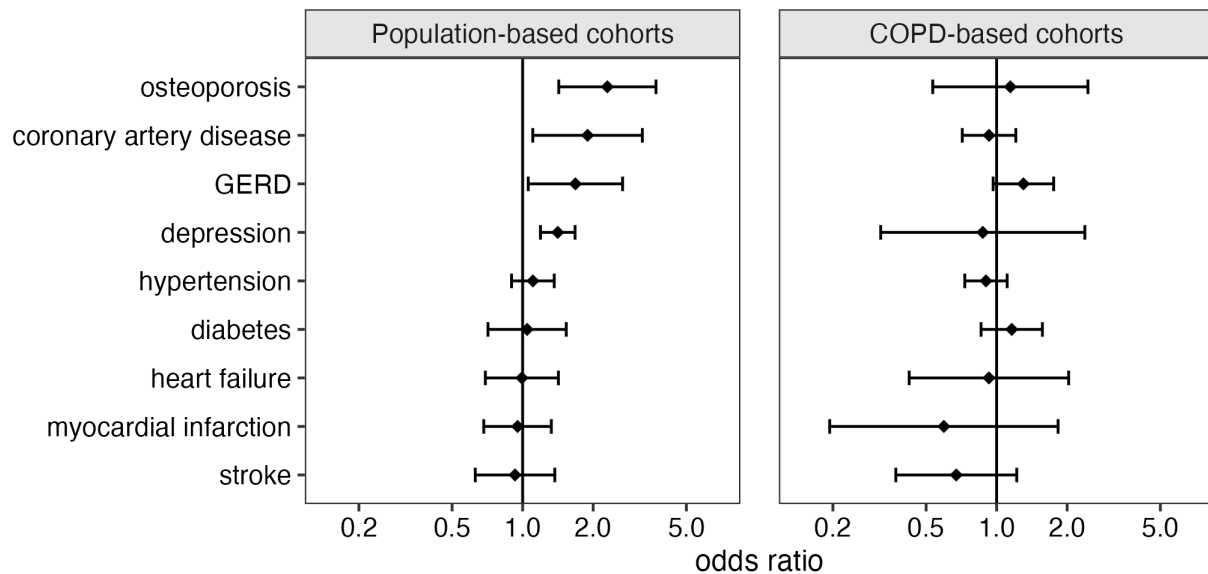
Table 1 Meta-analysed characteristics of AO compared with asthma-only and COPD-only in population-based and clinic-based cohorts

Characteristics	Population-based cohorts			Asthma-based cohorts			COPD-based cohorts		
	AO	Asthma-only	COPD-only	AO	Asthma-only	AO	Asthma-only	AO	COPD-only
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)	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)	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)	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)	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)	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)	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)	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)	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)	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)	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)	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)	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)	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)	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)	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)	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)	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)	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)	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)	3.0 (3.8)	3.7 (5.0)
Serum IgE (ie/mL), median (IQR)*	–	–	–	120 (292)	110 (221)	78 (192)	54 (116)	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.

A



B

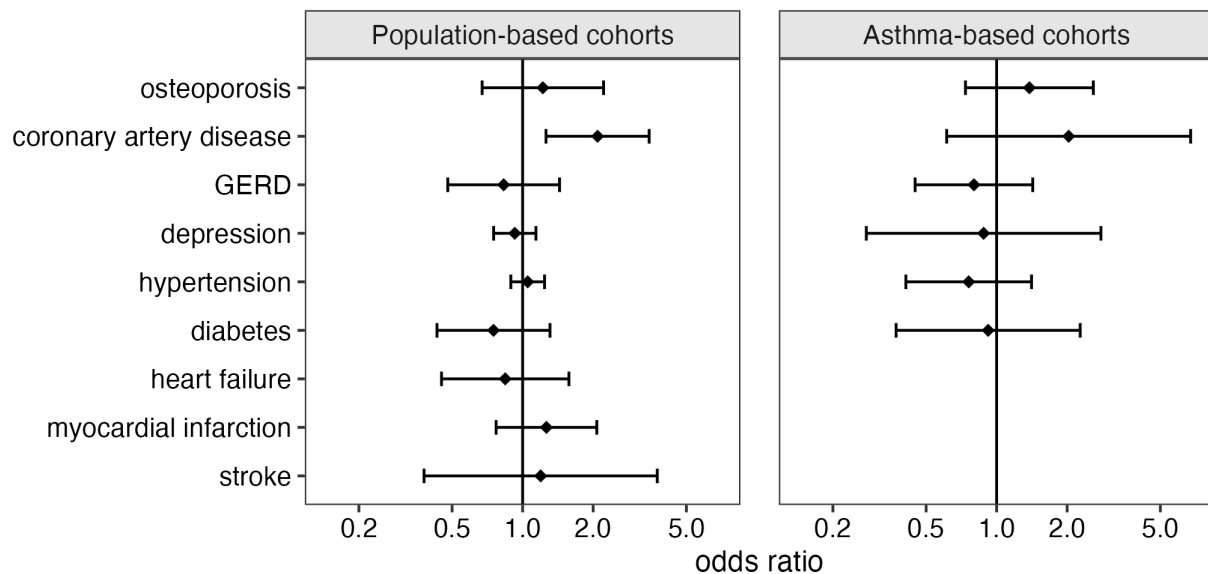


Figure 2 Meta-analysis of comorbidities among patients with asthma with airflow obstruction (AO) compared with COPD without a history of asthma (COPD-only) (A) and compared with asthma without airflow obstruction (asthma-only) (B). ORs were adjusted for age, sex, smoking status and body mass index. The 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 symptomatic 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 plugging³⁸ 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 FEV₁ 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 FEV₁<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 FEV₁ may partly explain these findings. A previous mendelian randomisation study provided evidence for an inverse relationship between FEV₁ and CAD.⁵⁰ FEV₁% 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 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.

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