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# Disease Burden of Eosinophilic Airway Disease: Comparing Severe Asthma, COPD and Asthma-COPD Overlap

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## Summary at a glance

This study investigated the disease burden associated with eosinophilic airway disease. We showed high disease burden in eosinophilic severe asthma, COPD and asthma-COPD overlap. In an era of precision medicine, understanding the disease burden of phenotypes is needed, particularly in asthma-COPD overlap where treatment evidence is limited.

## Abstract

**Background and objective**: There is less understanding of phenotypes and disease burden in asthma-COPD overlap (ACO) than either disease alone. Blood eosinophils may help identify the patients in the clinic with eosinophilic airway inflammation. The potential value of this approach requires an understanding of the illness burden associated with eosinophilic ACO, eosinophilic severe asthma and eosinophilic COPD, defined by blood eosinophils.

**Methods**: Participants from studies of multidimensional assessment in airway disease were pooled to identify patients with ACO (N=106), severe asthma (N=64) and COPD alone (N=153). Patients were assessed cross-sectionally for demographic and clinical characteristics, including disease burden indicators such as health-related quality of life (HRQoL) and past-year exacerbation. Eosinophilic patients were identified using different thresholds of blood eosinophil count.

**Results**: Using a blood eosinophil count $\geq 0.3\times10^9$/L, 41% had eosinophilic airway disease: 55% in ACO, 44% in severe asthma and 29% in COPD. Blood and sputum eosinophils were moderately correlated ($r_s$=0.51, N=257, $p$<.001). Burden of disease was similar between eosinophilic and non-eosinophilic airway disease, with poor HRQoL and high number of past-year exacerbations. Burden of disease was similar across eosinophilic severe asthma, COPD and ACO. Eosinophilic COPD tended to have poorer health status than eosinophilic ACO and severe asthma; however, in context of a high prevalence of eosinophilic ACO, cumulative population-level burden of eosinophilic disease was greater in ACO.

**Conclusions**: Disease burden across eosinophilic ACO, eosinophilic severe asthma and eosinophilic COPD was high, particularly cumulative population-level burden in ACO. Factors beyond airway inflammation may drive disease burden in severe patients.


**Short title**: Eosinophilic Airway Disease Burden

**Keywords**: Severe asthma, COPD, airway disease, treatable traits, precision medicine, eosinophilic airway inflammation, biomarker, blood eosinophils.

## Introduction

Around 20% of patients with obstructive airway disease have features of both asthma and chronic obstructive pulmonary disease (COPD); a group summarised as "asthma-COPD overlap" (ACO).[1] Although common, we know relatively little about this group of patients. They are often excluded from trials, so evidence to inform treatment decisions in this group is lacking.[2,3]

Understanding subtypes of obstructive airway disease and targeting treatment accordingly is a way forward in disease management. One of the best-characterised phenotypes, particularly in asthma, is eosinophilic airway inflammation. Management of asthma and COPD guided by sputum eosinophil counts is associated with substantial reductions in exacerbations and improved health status, compared to symptom-based management.[4,5] The gold standard assessment for eosinophilic airway inflammation is induced sputum; however, this is predominantly a research tool and translation into practice has proven difficult. A surrogate marker may be peripheral blood eosinophil count.[6-8] Blood eosinophils are associated with prognosis and treatment response in severe asthma and COPD.[9-12] In terms of implementing biomarker-driven treatment into clinical practice, the phenotype of eosinophilic inflammation defined by blood eosinophils currently shows the greatest potential. Yet, we know little about the prevalence and consequences of high blood eosinophil counts in ACO.

By estimating the disease burden of eosinophilic airway disease defined by blood eosinophils, we can gain insight into potential individual- and population-level gains from efficient phenotype-targeted treatments. Compared with asthma and severe asthma, there has been less investigation into the associations between blood eosinophils and disease burden in stable COPD, and even less still in ACO. Comparing the burden of eosinophilic ACO,

eosinophilic severe asthma and eosinophilic COPD may also help contextualise findings from phenotype-targeted treatments in different diagnostic groups, such as the limited success of anti-IL-5 monoclonal antibodies as therapy in eosinophilic COPD.[13,14] This study aimed to establish the illness burden associated with eosinophilic airway disease using multiple outcomes, and compare the disease burden of eosinophilic ACO, eosinophilic severe asthma and eosinophilic COPD. We hypothesised eosinophilic airway disease would be associated with increased disease burden for co-primary outcomes of health-related quality of life (HRQoL) and exacerbations, with little difference between eosinophilic ACO, eosinophilic severe asthma and eosinophilic COPD.

## Methods

### *Design*

Cross-sectional observational study.

### *Participants*

Patients were recruited via the respiratory ambulatory care clinics at John Hunter Hospital (Newcastle, Australia), clinical research databases and advertisement. Participants were adults (≥18 years) with confirmed diagnosis of COPD, severe asthma or ACO, and were stable in the prior four weeks. COPD was defined as persistent airflow limitation (post-bronchodilator forced expiratory volume in the first second [$FEV_1$]/forced vital capacity [FVC]<0.70). Severe asthma was defined according to the ERS/ATS Task Force definition.[15] ACO was defined as evidence of asthma (history of asthma diagnosis <40 years, documented bronchodilator reversibility on two occasions, and/or documented bronchial hyperresponsiveness) and evidence of persistent airflow limitation.[1,16] Current smokers (self-report or exhaled carbon monoxide >10ppm; N=20) and participants without valid full blood count results (N=22) were excluded.

### *Procedures*

This study is a secondary analysis of four studies of multidimensional phenotyping assessment conducted between April 2009 and August 2016, which have been previously described.[17-20] Composition and inclusion criteria of these cohorts are in Figure S1 and Table S1. The studies were conducted according to the principles of Good Clinical Practice. Participants provided written informed consent. Studies were approved by local institutional ethical review (Table S1). Briefly, airflow limitation was assessed by spirometry.[21] $FEV_1$ and FVC% predicted were calculated using NHANES III equations.[22] Sputum was induced using

a valid protocol and differential cell counts were performed.[23] Full blood counts and serum high-sensitivity C-reactive protein were performed using standardised methods from peripheral blood samples. In a subset, fractional inhaled nitric oxide (FeNO) was measured. Patients completed questionnaires, including St George's Respiratory Questionnaire (SGRQ),[24] Hospital Anxiety and Depression Scale,[25] Modified Medical Research Council scale for functional limitation due to dyspneoa.[26] Smoking history was self-reported and confirmed by exhaled carbon monoxide. Past-year exacerbations were self-reported and defined as a COPD or asthma-related episode that led to hospitalisation, emergency department visit, or oral corticosteroids (OCS) for at least 3 days,[27,28] or an exacerbation with lower respiratory tract infection requiring antibiotics.[29] Comorbidities and medication use were determined through medical history. Prognostic indices were calculated: Charlson Comorbidity Index[30] and BODE (Body-Mass Index, Airflow Obstruction, Dyspnoea and Exercise Capacity Index).[31] Past-week adherence to preventer medications was self-reported. To assess exercise limitation, 6-minute walk test was performed.[32]

***Statistical analysis***

Data were analysed using Stata 15/IC (Stata Corporation, College Station, Texas, USA) and $p < .05$ considered statistically significant. Equality of distributions of blood eosinophils across ACO, severe asthma and COPD was examined via Kolmogorov-Smirnov test. Prevalence of eosinophilia was calculated using different blood eosinophil thresholds and sputum eosinophils ≥3%, and compared across diagnoses via chi-squared test. Multinomial logistic regression was conducted to estimate the likelihood of severe asthma or COPD, compared with ACO, in eosinophilic patients ($\geq 0.3\times10^9$/L). Spearman's correlations between blood and sputum eosinophils were conducted. Receiver operating characteristics (ROC) area under the curve (AUC) analysis was completed to examine whether blood eosinophils predicted ≥3%

sputum eosinophils. Characteristics of eosinophilic (defined as blood eosinophils $\geq 0.3\times10^9$/L) and non-eosinophilic airway disease were compared via independent-samples t-test, chi-squared, Fisher's exact or Wilcoxon-Mann Whitney test, as appropriate. This blood eosinophil threshold was selected for consistency with previous literature and because it was the optimal empirical cut-off for categorising ≥3% sputum eosinophils in the current sample using ROC analysis (sensitivity 0.64; specificity 0.81). Disease burden measures of eosinophilic ACO, severe asthma and COPD were compared via one-way analysis of variance, chi-squared, Fisher's exact, or Kruskal–Wallis, and Tukey post-hoc tests completed as required. We wanted to illustrate the population-level burden of disease attributable to eosinophilic ACO, severe asthma and COPD, compared with the burden of non-eosinophilic airway inflammation in each disease. To do this, we multiplied the number of patients per 100 with eosinophilic inflammation (proportion in each disease category) by the median number of exacerbations in the eosinophilic inflammation group. We did this for each diagnosis group – ACO, severe asthma and COPD – separately. We repeated this procedure with non-eosinophilic inflammation population (proportion x median exacerbations) and graphed both eosinophilic and non-eosinophilic burden for each disease. The figure then illustrates the total number of exacerbations for 100 patients with either ACO, severe asthma or COPD, then splits this number into the part attributable to eosinophilic and non-eosinophilic inflammation. We then repeated this for the outcomes of health status (SGRQ mean total score) and proportion of maintenance OCS users. Calculations are reported in Table S2.

## Results

*Prevalence of eosinophilic airway disease*

Of the 323 participants included in the study, 106 had ACO, 64 had severe asthma alone and 153 had COPD alone. Distributions of eosinophils were right skewed, and the distribution

pattern significantly differed between ACO and COPD (p<.001; Figure 1). Blood eosinophil count ≥0.3x$10^9$/L was observed in 41% of patients with airway disease, with prevalence highest in ACO and lowest in COPD (Figure 2; Table S3). The pattern was similar using different thresholds of blood eosinophils or ≥3% sputum eosinophils, except at ≥0.2x$10^9$/L. Patients with blood eosinophil count ≥0.3x$10^9$/L were less likely to have COPD alone than ACO (relative risk ratio [RRR]=0.34, 95%CI 0.21-0.58, *p*<.001), but no more likely to have severe asthma alone than ACO (RRR=0.64, 95%CI 0.34-1.20, *p*=.167).

*Correlation between blood and sputum eosinophils*

Sputum and blood eosinophils were significantly correlated in the whole cohort ($r_s$=0.51, N=257, *p*<.001; Figure 3A). The correlation was larger in severe asthma ($r_s$=0.64, N=49, *p*<.001), than COPD ($r_s$=0.43, N=122, *p*<.001) and ACO ($r_s$=0.42, N=86, *p*<.001). In a subset, there was a weak, significant correlation between FeNO and blood eosinophils ($r_s$=0.31, N=139, *p*<.001).

Blood eosinophil count predicted sputum count ≥3% (AUC=0.76, 95%CI 0.70-0.82; Figure 3B). Prediction was best in severe asthma (AUC=0.84, 95%CI 0.73-0.95). Lower AUC were observed in ACO (AUC=0.71, 95%CI 0.60-0.82) and COPD (AUC=0.75, 95%CI 0.66-0.84). There was generally concordance between blood eosinophils at ≥0.3x$10^9$/L and sputum eosinophils ≥3%, with 72% correctly classified (Table S4). Concordance was greatest in severe asthma. In ACO, true positives (both blood and sputum indicate eosinophilia) were more common and in COPD, true negatives (both blood and sputum indicate no eosinophilia) were more common.

*Burden of eosinophilic airway disease*

There were few statistically significant differences in demographic characteristics, clinical characteristics and health burden between non-eosinophilic and eosinophilic phenotypes in the combined airway disease cohort (Table 1). Both phenotypes had similar HRQoL impairment (SGRQ total score), much greater than published norms,[33] although patients with eosinophilic airway disease reported higher scores on the symptoms subscale. Both groups had a median of two past-year exacerbations, although patients with eosinophilic disease were more likely to experience exacerbations requiring OCS. Eosinophilic patients used more respiratory medications and a higher dose of ICS. Sensitivity analyses using blood eosinophils $\geq 0.5\times10^9$/L and sputum eosinophils ≥3% showed a largely similar pattern of results.

*Burden of eosinophilic ACO, severe asthma and COPD*

Patients had high disease burden that was largely similar in magnitude across groups, indicated in HRQoL, past-year exacerbations and comorbidity measures (Table 2). Patients with eosinophilic ACO had significantly more past-year exacerbations, particularly exacerbations requiring OCS, than eosinophilic severe asthma. Exacerbations requiring OCS and comorbidity indices were greater in eosinophilic COPD than eosinophilic severe asthma. Suboptimal adherence (<80% of prescribed treatment) was far more common in eosinophilic severe asthma than eosinophilic COPD or ACO. Data for non-eosinophilic ACO, severe asthma and COPD are provided in Table S5 for comparison.

For 100 patients with ACO, the cumulative number of past-year exacerbations in eosinophilic disease was 164 (Figure 4A; Table S2). This number was much higher than in severe asthma and COPD (44 and 59, respectively). Eosinophilic disease contributed to around half of the

OCS burden in ACO and severe asthma (Figure 4B; Table S2). For 100 patients, the cumulative SGRQ score attributable to eosinophilic airways disease in ACO was 2872.8, which was higher than in severe asthma (1942.5) or COPD (1638.1) (Figure 4C; Table S2).

## Discussion

Eosinophilic inflammation was common in patients with stable severe asthma, COPD and ACO. Patients with eosinophilic and non-eosinophilic airway disease had similar clinical characteristics and high disease burden across multiple indicators. Patients with eosinophilic severe asthma, eosinophilic COPD and eosinophilic ACO had equally poor health status, although patients with eosinophilic ACO had more past-year exacerbations and eosinophilic COPD had more comorbidity and exercise limitation. Since the prevalence of eosinophilia was highest in ACO, the cumulative health burden of eosinophilia at a population-level was greatest in ACO. This study supports an eosinophilic phenotype across the disease labels of severe asthma and COPD, and their overlap. The high disease burden of eosinophilic ACO and the potential for new treatments to have effects in this group highlight this subset of patients as an important group for further study.

Eosinophilia defined as a blood eosinophil count $\geq 0.3 \times 10^9$/L was present in 41% of patients with airway disease, and was most common in ACO followed by severe asthma and COPD. Prevalence was similar using a 3% sputum threshold. Published estimates of eosinophilia in ACO are uncommon, although available figures are similar, with eosinophilic or mixed eosinophilic/neutrophilic bronchitis observed in 45% of stable ACO, 42% of stable asthma and 25% of stable COPD.[34] The pattern of prevalence across diseases was largely comparable using alternative thresholds of blood eosinophils, except at $\geq 0.2 \times 10^9$/L where eosinophilia prevalence was similar in severe asthma and COPD. Studies indicate a threshold of $\geq 0.2 \times 10^9$/L is sensitive at ruling out sputum eosinophilia in stable COPD;[7] however, at this threshold the presence of airway eosinophilia may be overestimated. In the current study, eosinophilia was prevalent despite most patients being on ICS/LABA and some on maintenance OCS. There are multiple possible explanations. First, ICS may not reduce blood

eosinophils. There is limited evidence on this issue, however in a small consecutive case series of moderate-severe asthma, doubling ICS dose (1000 to 2000µg beclomethasone equivalent/day) reduced blood eosinophil counts by almost half (0.56 to $0.32 \times 10^9$/L).[35] Secondly, patients may be refractory to treatment, resulting in eosinophilia and residual symptoms despite corticosteroid treatment. Finally, observed eosinophilia may be illustrative of longer-term patterns of adherence not captured in the current study. Suboptimal adherence was more common in eosinophilic severe asthma, compared with ACO and COPD. This indicates heterogeneity among patients with eosinophilia, supporting a need to assess patients across multiple domains.

In this study, patients with eosinophilic airway disease were often former smokers with significant pack-years, had demonstrated airflow limitation, a median two past-year exacerbations, and substantial HRQoL impairment and comorbidity. Contrary to our hypothesis, we did not observe increased disease burden in eosinophilic airway disease. However, in the context of high population prevalence of eosinophilic inflammation, eosinophilic airway disease at a population-level contributes to a greater cumulative burden in HRQoL and exacerbations than non-eosinophilic disease, particularly for ACO. Similar health burden between eosinophilic and non-eosinophilic disease has been observed previously in unselected asthma, COPD and their overlap.[36-38] Other studies demonstrate differences between eosinophilic and non-eosinophilic airways disease in some but not all measures.[10,12,39] Perhaps eosinophilia, which differentiates disease burden in asthma,[39] may no longer be a valuable indicator of burden when the spectrum of airway disease is broadened to include COPD and ACO, or focuses on severe asthma. Our sample may represent a narrow and severe spectrum of disease, such that the patient's overall health burden masks any effect of eosinophilia. Alternatively, patients were on high dose ICS, so we may be observing

treatment refractory eosinophilia, which may be equally burdensome as non-eosinophilic disease. Finally, it may be that there is genuinely no difference between eosinophilic and non-eosinophilic airway disease and other characteristics are more predictive of health burden, including extrapulmonary characteristics.

Patients with eosinophilic ACO have seldom been described. Despite high prevalence of ACO, these patients are typically excluded from clinical trials.[2,3] Therefore, there is limited evidence to guide treatment decisions in these patients. Patients with eosinophilic ACO have poor HRQoL, comorbidity, a median of 3 past-year exacerbations, take a median of 3.5 respiratory medications and 19% are on maintenance OCS. Exacerbations were particularly high in this group, which is important when exacerbations are a key clinical endpoint for new therapeutics. Besides having the most exacerbations, in terms of disease burden they appear to be somewhere in the middle of eosinophilic severe asthma and COPD. Previous studies not selecting for eosinophilia indicate ACO generally has a greater health burden, particularly increased exacerbations, compared to COPD or asthma alone.[40,41]

Limitations of this study include the cross-sectional nature. Prospective longitudinal evidence would evidence stability of phenotypes, diagnosis groups and disease burden over time. Classification of eosinophilia was based on a single measurement of blood eosinophils, where multiple measurements may provide more accurate phenotype classification.[42] The non-eosinophilic group likely included a mix of patients with treated eosinophilia and patients without eosinophilia regardless of treatment, which is a limitation to consider when interpreting the disease burden estimates in this group. We used a pragmatic definition of ACO since it could be easily translated into practice. Alternatives have been proposed and

used in previous studies,[16,41] which may have produced discrepant results. Exacerbations were based on participant recall.

The use of blood eosinophils in airway disease is an important area of investigation, particularly in an era of precision medicine where biomarkers can be used to individualise treatments. This study contributes to a better understanding of complexity and heterogeneity in ACO, severe asthma and COPD; all are patient groups with high healthcare utilisation. Until recently there was limited recognition of eosinophilic COPD and few data exist examining the impact it has on clinical outcomes; even less in ACO. With increased recognition of eosinophils in airway diseases, it builds support to suggest treatments considered in one disease be considered in others based on phenotype.

In conclusion, patients with eosinophilic airways disease classified via blood eosinophils demonstrated similar characteristics to non-eosinophilic disease and had high disease burden. Eosinophilic ACO, severe asthma and COPD were similar in health burden, although eosinophilic COPD tended to have poorer health status and eosinophilic ACO more exacerbations. At a population level, the greatest cumulative health burden was in eosinophilic ACO, since eosinophilia was most prevalent in this group. This study supports eosinophilia as a phenotype that spans across disease labels of severe asthma and COPD, and their overlap.

## Author Contributions

All authors contributed to developing the study design, data interpretation, and critical review and revision of the manuscript. SAH conducted the data analysis and first draft of the manuscript. VMM and PGG acquired the data, as chief investigators on the original primary studies. All authors approved the final version of the manuscript. VMM is guarantor taking responsibility for the integrity of the manuscript, from inception to publication.

## Disclosure statement

This study was supported by an investigator initiated grant from AstraZeneca (ESR-16-12552). The funder was not involved in data collection, analysis, or interpretation; trial design; patient recruitment; or any aspect pertinent to the study. **Sarah A. Hiles'** salary during the conduct of the study was supported by a grant from AstraZeneca (ESR-16-12552) paid to her employer (University of Newcastle). **Peter G. Gibson** has received research grants and speaker fees from AstraZeneca, GlaxoSmithKline and Novartis. **Vanessa M. McDonald** has received speaker fees for unrelated work, grants for organising education unrelated work, and research funds for unrelated work from AstraZeneca, Menarini and GlaxoSmithKline.

## Figure captions

Figure 1. Distribution of peripheral blood eosinophils among diagnosis groups of asthma-COPD overlap (ACO), severe asthma alone and COPD alone. The distribution of eosinophils differed between ACO and COPD (D=0.29, p<.001); but not ACO and severe asthma (D=0.18, p=.166).

Figure 2. Proportion of eosinophilic patients using different blood eosinophil count thresholds and ≥3% sputum cell count. * $p < .05$; ** $p < .01$; *** $p < .001$. The numeric values are available in the online supplement Table S3.

Figure 3. Associations between blood and sputum eosinophils in (A) ACO, (B) severe asthma alone, and (C) COPD alone. (D) Receiver operating characteristics (ROC) curve for blood eosinophil level predicting sputum eosinophils ≥3% in the whole cohort; area under the curve (AUC) 0.76, 95%CI 0.70-0.82, N=257.

Figure 4. Burden per 100 patients of (A) number of exacerbations, (B) maintenance oral corticosteroid use, and (C) St George's Respiratory Questionnaire scores in ACO, severe asthma and COPD; compared between eosinophilic disease (black) and non-eosinophilic disease (grey). The numeric values and calculations are available in the online supplement Table S2.

Table 1. Characteristics of eosinophilic and non-eosinophilic airway disease, where eosinophilic was defined as blood count ≥0.3x$10^9$/L.

| | **Non-eosinophilic airway disease N = 192** | **Eosinophilic airway disease N = 131** | ***p*** |
|---|---|---|---|
| **Demographic and clinical characteristics** | | | |
| Age (years), mean (SD) [range] | 65.8 (12.6) [19-89] | 63.2 (13.3) [25-87] | .077 |
| Females, % | 92 (47.9) | 69 (52.7) | .401 |
| Former smoker, % | 139 (72.8) | 83 (64.3) | .108 |
| Pack years (ex-smokers), median (IQR) | 38.8 (18.0, 63.0) | 33.0 (8.8, 52.0) | .061 |
| Blood eosinophils (count x$10^9$/L), median (IQR) | 0.1 (0.1, 0.2) | 0.4 (0.3, 0.6) | <.001 |
| Sputum eosinophils %, median (IQR) | 1.0 (0.5, 3.0) | 6.2 (2.3, 16.8) | <.001 |
| CRP (mg/L), median (IQR) | 3.4 (1.8, 8.2) | 3.5 (1.9, 8.1) | .710 |
| Pre-BD, mean (SD) | | | |
| FEV1 % predicted | 59.4 (23.0) | 57.9 (21.4) | .580 |
| FVC % predicted | 77.7 (18.0) | 76.8 (17.0) | .654 |
| FER | 0.6 (0.2) | 0.6 (0.2) | .858 |
| Post-BD, mean (SD) | | | |
| FEV1 % predicted | 62.0 (22.6) | 60.9 (21.1) | .637 |
| FVC % predicted | 79.3 (18.0) | 79.4 (16.3) | .945 |
| FER | 0.6 (0.2) | 0.6 (0.2) | .910 |
| Reversibility of airflow limitation (mL change in FEV1 after BD), mean (SD) | 68.5 (107.6) | 71.4 (121.3) | .822 |
| **Health burden indices** | | | |
| SGRQ, mean (SD) | | | |
| Total | 50.6 (17.2) | 51.9 (19.5) | .535 |
| Symptoms | 58.2 (21.3) | 64.8 (22.6) | .010 |
| Activity | 66.6 (22.3) | 66.1 (23.4) | .820 |
| Impacts | 39.1 (19.1) | 39.8 (20.2) | .764 |

| | | | |
|---|---|---|---|
| Total exacerbations, median (IQR) | 2.0 (1.0, 3.0) | 2.0 (1.0, 5.0) | .186 |
| OCS courses | 1.0 (0.0, 1.0) | 1.0 (1.0, 2.0) | .025 |
| Antibiotic courses | 2.0 (1.0, 3.0) | 2.0 (1.0, 4.0) | .551 |
| BMI (kg/m$^2$), mean (SD) | 31.1 (8.2) | 29.9 (7.0) | .156 |
| BODE, median (IQR) | 3.0 (1.0, 5.0) | 3.0 (1.0, 4.0) | .668 |
| CCI, median (IQR) | 3.0 (1.0, 5.0) | 3.0 (0.0, 4.0) | .264 |
| HADS, mean (SD) | 11.9 (7.4) | 12.4 (6.7) | .555 |
| Dyspnoea score, median (IQR) | 2.0 (1.0, 3.0) | 2.0 (1.0, 3.0) | .741 |
| Total walk distance, mean (SD) | 429.0 (122.3) | 434.4 (111.1) | .769 |
| **Medication use** | | | |
| Number of respiratory medications, median (IQR) * | 3.0 (2.0, 3.0) | 3.0 (3.0, 4.0) | .001 |
| ICS, % | 164 (85.4) | 122 (93.1) | .033 |
| ICS derived daily dose (beclomethasone equivalent) of current users, median (IQR) | 2000.0 (1000.0, 2000.0) | 2000.0 (2000.0, 2000.0) | .003 |
| LABA, % | 166 (86.5) | 122 (93.1) | .058 |
| LAMA, % | 143 (74.5) | 87 (66.4) | .116 |
| Omalizumab, % | 2 (1.0) | 5 (3.8) | .124 |
| Mepolizumab, % | 4 (2.1) | 0 (0) | .150 |
| Maintenance OCS, % | 22 (11.5) | 23 (17.6) | .120 |
| OCS derived daily dose (prednisone equivalent) of current users, median (IQR) | 10.0 (5.0, 15.0) | 8.0 (5.0, 10.0) | .679 |
| Preventer adherence <80%, % | 22 (12.0) | 15 (12.6) | .880 |

* Medications were SABA, LABA, LTRA, SAMA, LAMA, nasal steroids, theophylline, maintenance OCS, ICS, ICS/LABA, omalizumab, mepolizumab.

Abbreviations: BD: bronchodilator; BMI: body mass index; BODE: Body-Mass Index, Airflow Obstruction, Dyspnoea and Exercise Capacity Index; CCI: Charlson Comorbidity Index; CRP: C-reactive protein; FER: forced expiratory ratio; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; HADS: Hospital Anxiety and Depression Scale; ICS: inhaled corticosteroid; IQR: interquartile range; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonists; OCS:

oral corticosteroid; SABA: short-acting beta agonist; SAMA: short-acting muscarinic antagonist; SD: standard deviation; SGRQ: St George's Respiratory Questionnaire.

Table 2. Burden of eosinophilic ACO, severe asthma and COPD, defined as blood eosinophils count ≥0.3x$10^9$/L.

| | **Eosinophilic ACO** | **Eosinophilic severe asthma** | **Eosinophilic COPD** | ***P (overall unadjusted)*** |
|---|---|---|---|---|
| | **N = 58** | **N = 28** | **N = 45** | |
| Age, mean (SD) [range] | 60.2 (14.4) [a] [25-83] | 56.9 (11.8) [b] [29-74] | 71.0 (8.3) [a,b] [44-87] | <.001 |
| Females, N (%) | 32 (55.2) | 19 (67.9) | 18 (40.0) | .060 |
| Former smoker, % | 39 (67.2) [a] | 8 (30.8) [a,b] | 36 (80.0) [b] | <.001 |
| Pack years (ex-smokers), median (IQR) | 38.8 (7.5, 52) | 17.0 (4.3, 26.7) | 35.3 (10.6, 61.9) | .214 |
| Reversibility of airflow limitation (mL change in FEV1 after BD), mean (SD) | 71.4 (130.7) | 66.7 (122.2) | 74.5 (109.5) | .967 |
| SGRQ, mean (SD) | | | | |
| Total | 52.5 (21.0) | 44.4 (17.2) | 55.7 (17.6) | .060 |
| Symptoms | 68.2 (21.9) | 57.4 (23.9) | 64.5 (22.2) | .132 |
| Activity | 64.3 (25.2) | 58.4 (19.0) [a] | 73.1 (21.6) [a] | .027 |
| Impacts | 40.8 (21.4) | 32.3 (18.8) | 43.0 (18.7) | .091 |
| Total exacerbations, median (IQR) | 3.0 (1.0, 6.0) [a] | 1.0 (0.0, 3.0) [a] | 2.0 (1.0, 4.0) | .012 |
| OCS courses | 1.0 (1.0, 2.0) [a] | 1.0 (0.0, 1.0) [a,b] | 2.0 (0.0, 3.0) [b] | .006 |
| Antibiotic courses | 2.0 (1.0, 4.0) | 1.0 (0.0, 3.0) | 2.0 (1.0, 3.5) | .277 |
| BMI, mean (SD) | 29.3 (6.8) | 30.3 (5.8) | 30.5 (8.0) | .664 |
| BODE, median (IQR) | 3.0 (2.0, 4.0) | 2.0 (1.0, 3.0) [a] | 4.5 (3.0, 5.0) [a] | .001 |
| CCI, median (IQR) | 3.0 (0.0, 4.0) [a] | 0.0 (0.0, 3.0) [b] | 4.0 (4.0, 5.0) [a,b] | <.001 |
| Total walk distance, mean (SD) | 439.3 (98.6) | 461.1 (95.1) [a] | 371.9 (148.3) [a] | .048 |

| | | | | |
|---|---|---|---|---|
| Dyspnoea score, median (IQR) | 1.0 (1.0, 4.0) | 2.0 (1.0, 3.0) | 2.0 (2.0, 3.0) | .107 |
| HADS, mean (SD) | 12.4 (7.3) | 12.9 (6.2) | 12.0 (6.2) | .883 |
| Number of respiratory medications, median (IQR) * | 3.5 (3.0, 4.0) | 3.0 (3.0, 4.0) | 3.0 (3.0, 4.0) | .051 |
| ICS, N (%) | 55 (94.8) | 28 (100.0) | 39 (86.7) | .088 |
| ICS derived daily dose (beclomethasone equivalent) of current users, median (IQR) | 2000.0 (2000.0, 2000.0) | 2000.0 (2000.0, 2000.0) | 2000.0 (1000.0, 2000.0) | .279 |
| LABA, N (%) | 56 (96.6) | 27 (96.4) | 39 (86.7) | .116 |
| LAMA, N (%) | 39 (67.2) [a,b] | 7 (25.0) [a,c] | 41 (91.1) [b,c] | <.001 |
| Omalizumab, N (%) | 4 (6.9) | 1 (3.6) | 0 (0) | .225 |
| Mepolizumab, N (%) | 0 | 0 | 0 | N/A |
| Maintenance OCS, N (%) | 11 (19.0) [a] | 11 (39.3) [b] | 1 (2.2) [a,b] | <.001 |
| OCS derived daily dose (prednisone equivalent) of current users, median (IQR) | 5.0 (5.0, 10.0) | 8.0 (8.0, 20.0) | 4.0 (4.0, 4.0) | .207 |
| Preventer suboptimal adherence <80%, N (%) | 5 (9.4) [a] | 8 (30.8) [a,b] | 2 (5.0) [b] | .010 |

* Medications were SABA, LABA, LTRA, SAMA, LAMA, nasal steroids, theophylline, maintenance OCS, ICS, ICS/LABA, omalizumab, mepolizumab.

% calculated on non-missing values. Letters are to denote $p < .05$ for post-hoc statistical tests comparing diagnostic groups.

Abbreviations: BMI: body mass index; BODE: Body-Mass Index, Airflow Obstruction, Dyspnoea and Exercise Capacity Index; CCI: Charlson Comorbidity Index; HADS: Hospital Anxiety and Depression Scale; IQR: interquartile range; OCS: oral corticosteroid; SD: standard deviation; SGRQ: St George's Respiratory Questionnaire.

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Figure 1

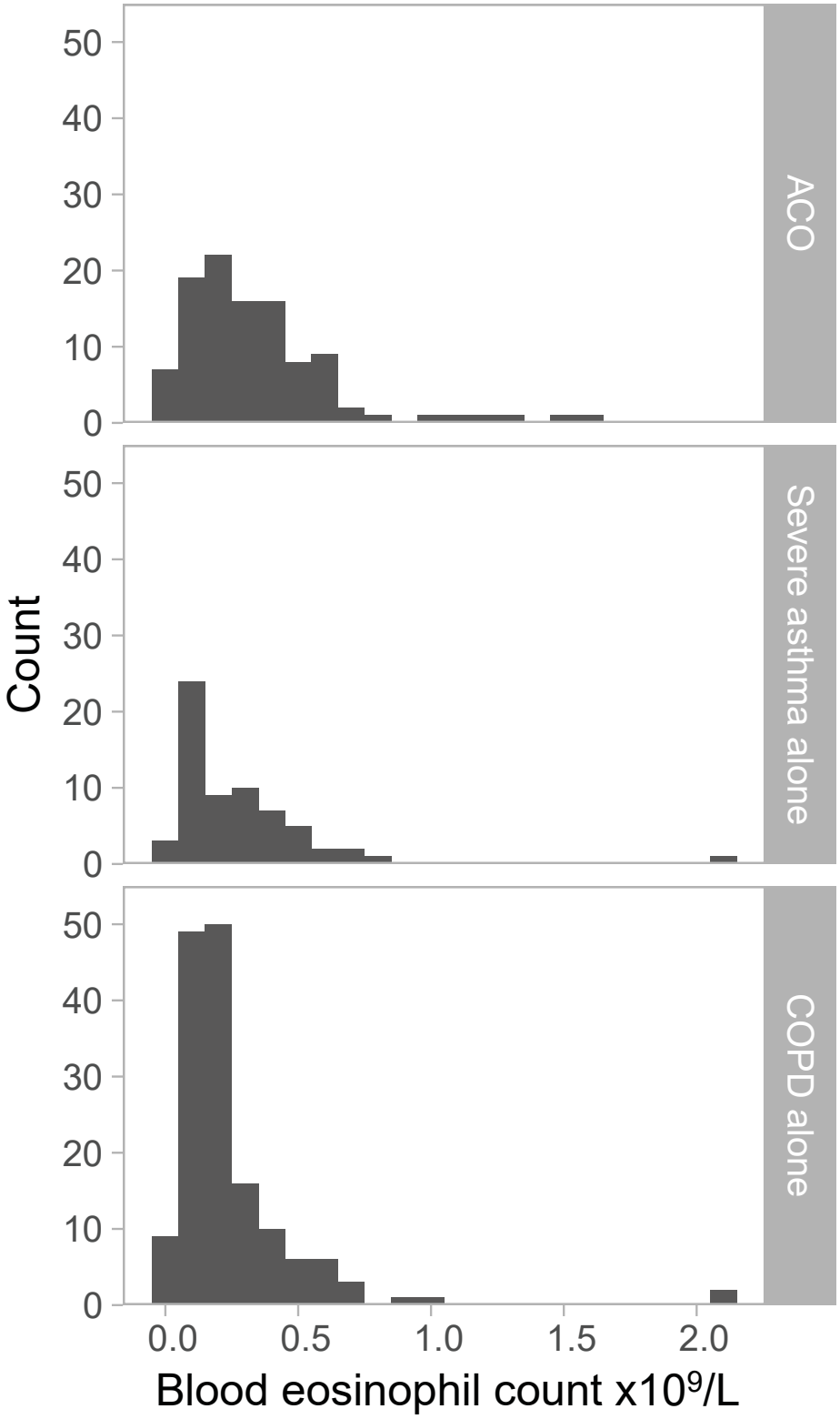
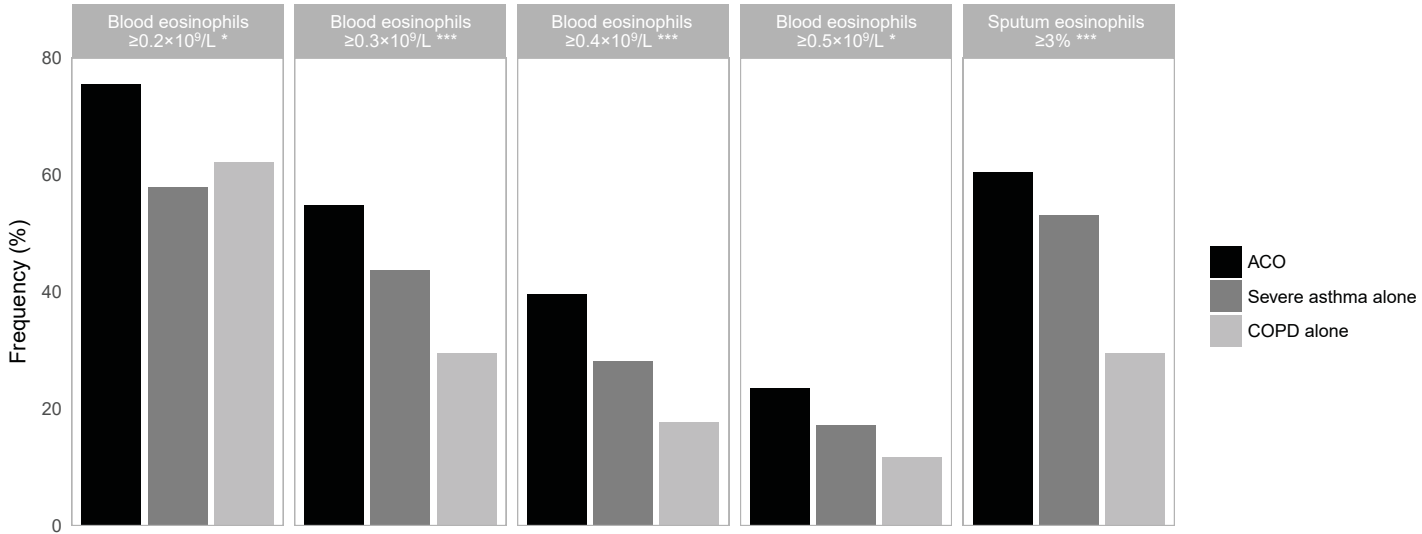

ACO
Severe asthma alone
COPD alone
Count
0
10
20
30
40
50
0.0
0.5
1.0
1.5
2.0
Blood eosinophil count x10⁹/L

Figure 2


Blood eosinophils ≥0.2×10⁹/L *
Blood eosinophils ≥0.3×10⁹/L ***
Blood eosinophils ≥0.4×10⁹/L ***
Blood eosinophils ≥0.5×10⁹/L *
Sputum eosinophils ≥3% ***
Frequency (%)
0
20
40
60
80
ACO
Severe asthma alone
COPD alone

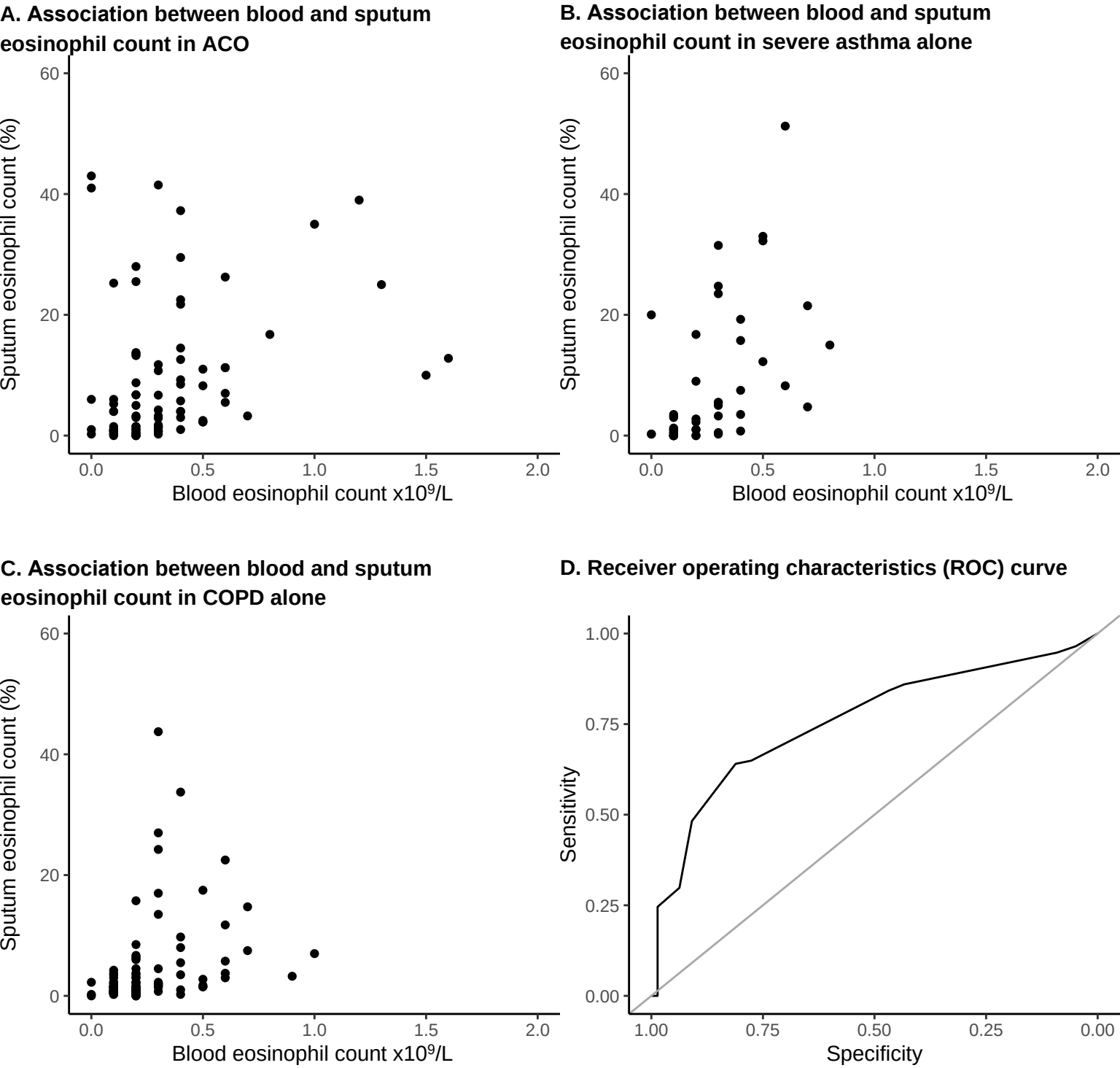
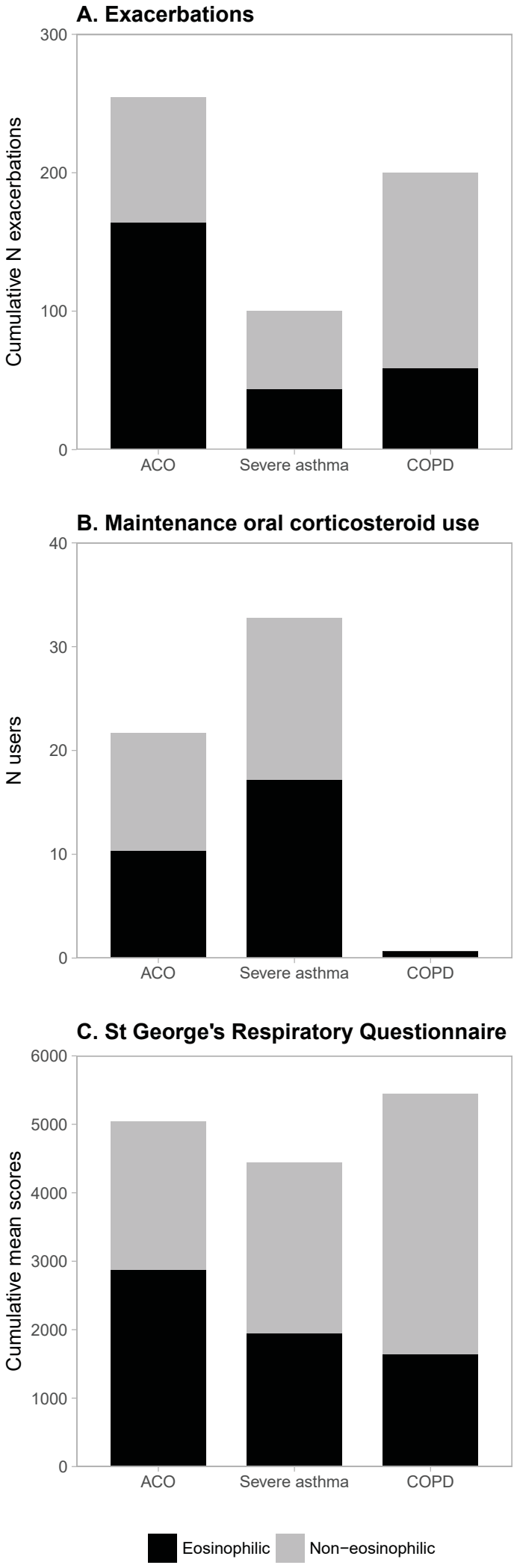

A. Association between blood and sputum eosinophil count in ACO
B. Association between blood and sputum eosinophil count in severe asthma alone
C. Association between blood and sputum eosinophil count in COPD alone
D. Receiver operating characteristics (ROC) curve
Sputum eosinophil count (%)
Blood eosinophil count x10⁹/L
Sensitivity
Specificity
0
20
40
60
0.0
0.5
1.0
1.5
2.0
0.00
0.25
0.50
0.75
1.00

Figure 4


A. Exacerbations
Cumulative N exacerbations
300
200
100
0
ACO
Severe asthma
COPD
B. Maintenance oral corticosteroid use
N users
40
30
20
10
0
ACO
Severe asthma
COPD
C. St George's Respiratory Questionnaire
Cumulative mean scores
6000
5000
4000
3000
2000
1000
0
ACO
Severe asthma
COPD
Eosinophilic
Non−eosinophilic

# SUPPLEMENTARY INFORMATION

**TITLE:** Disease Burden of Eosinophilic Airway Disease: Comparing Severe Asthma, COPD and Asthma-COPD Overlap

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**Figure S1.** Flow chart of participant selection from four phenotyping studies A (COPD)[1], B (severe asthma)[2], C (COPD)[3] and D (obstructive airway disease)[4] to final analysis sample for the current study (N=323). Note that the current study used data from participants screened for these studies, not only those that met inclusion criteria to enter the study. Abbreviations: ECO: exhaled carbon monoxide; ACO: asthma-COPD overlap.

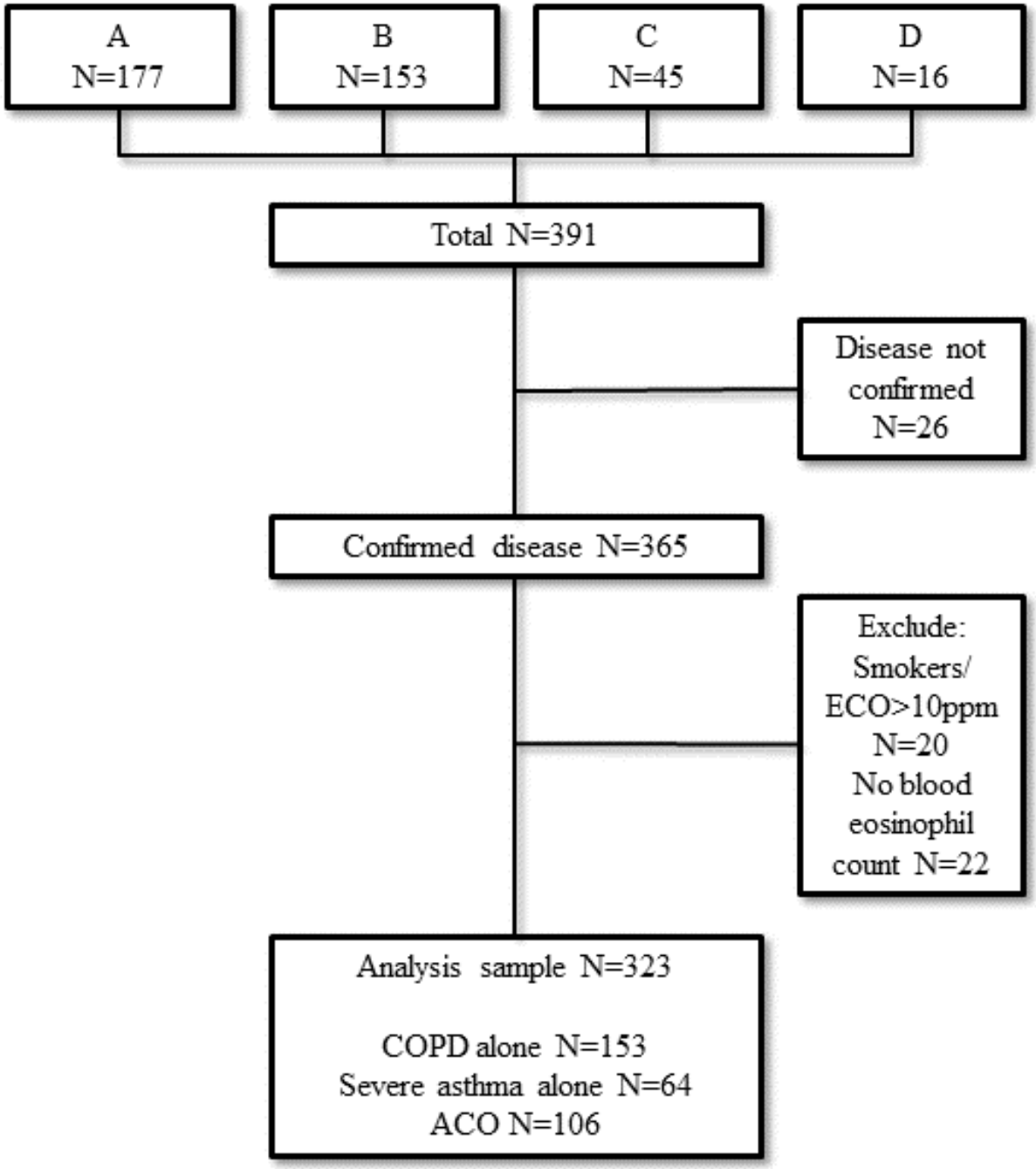

**Table S1**. Inclusion criteria for the target population of the original phenotyping/treatment studies. Note that the current study used data from participants screened for these studies, not only those that met inclusion criteria to enter the study. N reported here are in current study.

| **A** [1] **N = 150** | **B** [2] **N = 127** | **C** [3] **N = 34** | **D** [4] **N = 12** |
|---|---|---|---|
| Ethics: HNEHRC 12/12/12/3.06 | Ethics: HNEHRC 08/08/20/3.10 | Ethics: HNEHRC 08/08/20/3.10 | Ethics: HNEHRC 05/12/07/3.11 |
| Adults ≥18 years | Adults ≥18 years | Adults ≥55 years | Adults >55 years |
| COPD confirmed by incompletely reversible airflow obstruction (post-BD $FEV_1$ <80% predicted and FER <0.7 or physician confirmed COPD in patients with reduced FVC). GOLD Stage 2 or above. History of a prior acute COPD exacerbation in the past year. | Asthma confirmed by physician diagnosis, BDR (≥12%, 200mL), AHR or peak flow diurnal variation ≥15%. Maximal ICS therapy in combination with long acting beta-agonist or maintenance OCS use. Continuing poor asthma control (post-BD $FEV_1$ <80% predicted, or FER <0.7, or ACQ ≥1.5, or severe exacerbation requiring OCS in past 12 months). | COPD confirmed by airflow obstruction (pre-BD FER <0.7 and $FEV_1$ <80% predicted). | COPD and/or asthma based on symptoms, doctor diagnosis and spirometry. Asthma: episodic respiratory symptoms and fully reversible airflow obstruction with a post-BD FER ≥0.7 and post-BD $FEV_1$ >80% predicted, together with AHR or increased BDR (≥12%, 200mL). COPD: incompletely reversible airflow obstruction with a post-BD FER <0.7 and post-BD $FEV_1$ <80% predicted and no AHR or BDR. |
| Stable disease defined as no recent respiratory infection, acute exacerbation, or change in maintenance therapy in the previous 4 weeks. | Stable disease defined as no exacerbation in the last 4 weeks including any of the following: Hospital admission, emergency attendance, commencement of OCS or increased maintenance dose for acute symptoms or antibiotics for acute chest infection. | Stable disease defined as no increase in BD use, no use of OCS, no unscheduled doctor visit and no hospitalisation due to asthma or COPD in the past 4 weeks. | Stable disease with no exacerbation in past 4 weeks. |

ACQ: Asthma Control Questionnaire; AHR: airway hyperresponsiveness; BD: bronchodilator; BDR: bronchodilator response; COPD: chronic obstructive pulmonary disease; FER: forced expiratory ratio; $FEV_1$: forced expiratory volume in 1 second; FVC: forced vital capacity; ICS: inhaled corticosteroids; OCS: oral corticosteroids.

**Table S2**. Data underlying *Figure 4*: Burden per 100 patients of number of exacerbations, maintenance oral corticosteroid use, and St George's Respiratory Questionnaire (SGRQ) scores in ACO, severe asthma and COPD; compared between eosinophilic disease and non-eosinophilic disease. Calculated for each diagnosis group as: number of patients per 100 with either eosinophilic or non-eosinophilic inflammation in the diagnosis group (column A) multiplied by median/mean/proportion of patients with the outcome in either eosinophilic or non-eosinophilic disease (column B). Minor differences in burden value are due to rounding.

| Diagnosis | Group | N per 100 (A) | Outcome | Median/ mean/ proportion with outcome (B) | Cumulative burden value (A x B) |
|---|---|---|---|---|---|
| ACO | Eosinophilic | 54.7 | Exacerbation | 3 | 164.2 |
| Severe asthma | Eosinophilic | 43.8 | Exacerbation | 1 | 43.8 |
| COPD | Eosinophilic | 29.4 | Exacerbation | 2 | 58.8 |
| ACO | Non-eosinophilic | 45.3 | Exacerbation | 2 | 90.6 |
| Severe asthma | Non-eosinophilic | 56.3 | Exacerbation | 1 | 56.3 |
| COPD | Non-eosinophilic | 70.6 | Exacerbation | 2 | 141.2 |
| ACO | Eosinophilic | 54.7 | Maintenance OCS | 19.0% | 10.4 |
| Severe asthma | Eosinophilic | 43.8 | Maintenance OCS | 39.3% | 17.2 |
| COPD | Eosinophilic | 29.4 | Maintenance OCS | 2.2% | 0.65 |
| ACO | Non-eosinophilic | 45.3 | Maintenance OCS | 25.0% | 11.3 |
| Severe asthma | Non-eosinophilic | 56.3 | Maintenance OCS | 27.8% | 15.6 |
| COPD | Non-eosinophilic | 70.6 | Maintenance OCS | 0% | 0 |
| ACO | Eosinophilic | 54.7 | SGRQ | 52.5 | 2872.8 |
| Severe asthma | Eosinophilic | 43.8 | SGRQ | 44.4 | 1942.5 |
| COPD | Eosinophilic | 29.4 | SGRQ | 55.7 | 1638.1 |
| ACO | Non-eosinophilic | 45.3 | SGRQ | 47.8 | 2163.9 |
| Severe asthma | Non-eosinophilic | 56.3 | SGRQ | 44.4 | 2497.2 |
| COPD | Non-eosinophilic | 70.6 | SGRQ | 53.9 | 3805.7 |

**Table S3.** Data underlying *Figure 2*: Proportion of eosinophilic patients using different blood eosinophil count thresholds and ≥3% sputum cell count.

| Threshold | ACO (%) | Severe asthma alone (%) | COPD alone (%) |
|---|---|---|---|
| Blood eosinophils ≥$0.2\times10^9$/L | 75.5 | 57.8 | 62.1 |
| Blood eosinophils ≥$0.3\times10^9$/L | 54.7 | 43.8 | 29.4 |
| Blood eosinophils ≥$0.4\times10^9$/L | 39.6 | 28.1 | 17.7 |
| Blood eosinophils ≥$0.5\times10^9$/L | 23.6 | 17.2 | 11.8 |
| Sputum eosinophils ≥3% | 60.5 | 53.1 | 29.5 |

**Table S4**. Concordance between blood and sputum eosinophils (percentages are cell frequency).

| | **Blood eosinophils $<0.3\times10^9$/L** | **Blood eosinophils $\geq0.3\times10^9$/L** |
|---|---|---|
| **Overall** | | |
| **Sputum eosinophils <3%** | 111 (43.2%) | 32 (12.5%) |
| **Sputum eosinophils ≥3%** | 40 (15.6%) | 74 (28.8%) |
| **ACO** | | |
| **Sputum eosinophils <3%** | 22 (25.6%) | 12 (14.0%) |
| **Sputum eosinophils ≥3%** | 19 (22.1%) | 33 (38.4%) |
| **Severe asthma** | | |
| **Sputum eosinophils <3%** | 20 (40.8%) | 3 (6.1%) |
| **Sputum eosinophils ≥3%** | 6 (12.2%) | 20 (40.8%) |
| **COPD** | | |
| **Sputum eosinophils <3%** | 69 (56.6%) | 17 (13.9%) |
| **Sputum eosinophils ≥3%** | 15 (12.3%) | 21 (17.2%) |

**Table S5**. Burden of non-eosinophilic ACO, severe asthma and COPD, defined as blood eosinophils count < $0.3x10^9$/L.

| | **ACO** | **Severe asthma** | **COPD** | **P (*overall unadjusted*)** |
|---|---|---|---|---|
| | **N = 48** | **N = 36** | **N = 108** | |
| Age (years), mean (SD) [range] | 61.6 (12.4) [a] [27.8-79.6] | 57.5 (17.3) [b] [18.9-82.3] | 70.4 (8.0) [a,b] [50.7-88.6] | <.001 |
| Females, N (%) | 23 (47.9) | 22 (61.1) | 47 (43.5) | .187 |
| Former smoker, N (%) | 25 (52.1) [a] | 21 (58.3) [b] | 93 (86.9) [a,b] | <.001 |
| Pack years (ex-smokers), median (IQR) | 31.0 (9.3, 46.0) [a,b] | 9.0 (1.5, 17.0) [a,c] | 46.5 (32.5, 72.0) [b,c] | <.001 |
| Reversibility of airflow limitation (mL change in FEV1 after BD), mean (SD) | 81.5 (99.3) [a] | 20.0 (108.7) [a,b] | 79.6 (107.1) [b] | .010 |
| SGRQ, mean (SD) | | | | |
| Total | 47.8 (19.9) | 44.4 (17.7) [a] | 53.9 (14.9) [a] | .007 |
| Symptoms | 58.8 (21.6) | 59.8 (24.3) | 57.5 (20.4) | .833 |
| Activity | 60.4 (26.1) [a] | 54.9 (22.8) [b] | 73.3 (17.6) [a,b] | <.001 |
| Impacts | 37.5 (21.1) | 33.5 (18.0) | 41.7 (18.1) | .069 |
| Total exacerbations, median (IQR) | 2.0 (1.0, 5.0) [a] | 1.0 (0.0, 2.0) [a,b] | 2.0 (1.0, 3.0) [b] | <.001 |
| OCS courses | 1.0 (1.0, 1.0) | 1.0 (0.0, 1.0) [a] | 1.0 (0.0, 2.0) [a] | .013 |
| Antibiotic courses | 2.0 (1.0, 3.0) [a] | 1.0 (0.0, 2.5) [a,b] | 2.0 (1.0, 3.0) [b] | .003 |
| BMI, mean (SD) | 34.9 (9.8) [a] | 31.5 (8.1) | 29.4 (6.9) [a] | <.001 |
| BODE, median (IQR) | 2.0 (2.0, 4.0) [a] | 1.0 (1.0, 3.0) [b] | 5.0 (3.5, 6.0) [a,b] | <.001 |
| CCI, median (IQR) | 1.0 (0.0, 4.0) [a] | 0.0 (0.0, 3.0) [b] | 4.0 (3.0, 5.0) [a,b] | <.001 |
| Total walk distance, mean (SD) | 447.2 (106.8) [a] | 451.6 (130.9) [b] | 366.9 (114.4) [a,b] | .018 |
| Dyspnoea score, median (IQR) | 2.0 (1.0, 3.0) | 1.0 (1.0, 3.0) | 2.0 (1.0, 3.0) | .054 |
| HADS, mean (SD) | 12.3 (8.9) | 10.5 (5.8) | 12.2 (7.2) | .478 |
| Number of respiratory medications, median (IQR) * | 3.0 (3.0, 4.0) [a] | 3.0 (2.0, 4.0) | 3.0 (2.0, 3.0) [a] | .004 |
| ICS, % | 46 (95.8) [a] | 36 (100.0) [b] | 82 (75.9) [a,b] | <.001 |
| ICS derived daily dose (beclomethasone equivalent) of current users, median (IQR) | 2000.0 (2000.0, 2000.0) [a] | 2000.0 (2000.0, 2000.0) [b] | 1000.0 (1000.0, 2000.0) [a,b] | <.001 |

| | | | | |
|---|---|---|---|---|
| LABA, % | 46 (95.8) [a] | 36 (100.0) [b] | 84 (77.8) [a,b] | <.001 |
| LAMA, % | 31 (64.6) [a] | 15 (41.7) [b] | 97 (89.8) [a,b] | <.001 |
| Omalizumab, % | 1 (2.1) | 1 (2.8) | 0 (0) | .190 |
| Mepolizumab, % | 2 (4.2) | 2 (5.6) | 0 (0) | .035 |
| Maintenance OCS, % | 12 (25.0) [a] | 10 (27.8) [b] | 0 (0.0) [a,b] | <.001 |
| OCS derived daily dose (prednisone equivalent) of current users, median (IQR) | 10.0 (5.0, 25.0) | 5.0 (5.0, 15.0) | 0.0 (0.0, 0.0) | .267** |
| Preventer suboptimal adherence <80%, % | 4 (8.7) | 3 (9.7) | 15 (14.2) | .578 |

% calculated on non-missing values. Letters are to denote $p < .05$ for post-hoc statistical tests comparing diagnostic groups.

* Medications were SABA, LABA, LTRA, SAMA, LAMA, nasal steroids, theophylline, maintenance OCS, ICS, ICS/LABA, omalizumab, mepolizumab.
** Comparison of ACO and severe asthma only.

Abbreviations: BMI: body mass index; BODE: Body-Mass Index, Airflow Obstruction, Dyspnoea and Exercise Capacity Index; CCI: Charlson Comorbidity Index; HADS: Hospital Anxiety and Depression Scale; IQR: interquartile range; OCS: oral corticosteroid; SD: standard deviation; SGRQ: St George's Respiratory Questionnaire.

Examining the differences between Table 2 and Table S4, differences between eosinophilic and non-eosinophilic disease were minor. Ex-smokers were more common in patients with non-eosinophilic severe asthma compared with eosinophilic severe asthma, and more common in eosinophilic ACO compared with non-eosinophilic ACO. BMI was also greater and CCI was lower in non-eosinophilic ACO compared with eosinophilic ACO. ICS use was less frequent in non-eosinophilic COPD than eosinophilic COPD. LAMA use was more common in non-eosinophilic severe asthma than eosinophilic severe asthma. Suboptimal adherence was more common in eosinophilic severe asthma compared with non-eosinophilic severe asthma.

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