Early View

Review

Blood eosinophil counts in the general population and airways disease: a comprehensive review and meta-analysis

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Summary:

Blood eosinophil (EOS) counts are of interest as asthma/chronic obstructive pulmonary disease (COPD) treatment-response biomarkers. This comprehensive review describes EOS distributions/ranges published in asthma/COPD, controls and the general population.

Abstract

Background: The clinical context for using blood eosinophil (EOS) counts as treatment-response biomarkers in asthma and chronic obstructive pulmonary disease (COPD) requires better understanding of EOS distributions and ranges. We describe EOS distributions and ranges published in asthma, COPD, control (non-asthma/COPD) and general populations.

Methods: We conducted a comprehensive literature review and meta-analysis of observational studies (Jan 2008 to Nov 2018) that included EOS counts in asthma, severe asthma, COPD, control and general populations. Excluded studies had total sample sizes <200, EOS as inclusion criterion, hospitalised population only, exclusively paediatric participants.

Results: Overall, 91 eligible studies were identified, most had total-population-level data available: asthma (n=39 studies), severe asthma (n=12 studies), COPD (n=23 studies), control (n=7 studies), general populations (n=14 studies); some articles reported data for multiple populations. Reported EOS distributions were right-skewed (n=7 studies). Reported median EOS counts ranged from: asthma, 157–280 cells/µL (n=22 studies); severe asthma, 200–400 cells/µL (n=8 studies); COPD, 150–183 cells/µL (n=6 studies); controls, 100–160 cells/µL (n=3 studies); general populations, 100–200 cells/µL (n=6 studies). The meta-analysis showed observed variability was mostly between studies rather than within studies. Factors reportedly associated with higher blood EOS counts included: current smoking, positive skin prick test, elevated total IgE, comorbid allergic rhinitis, age ≤18 years, male sex, spirometric asthma/COPD diagnosis, metabolic syndrome and adiposity.

Conclusion: EOS distribution and range varied by study population, and were affected by clinical factors including age, smoking history and comorbidities which, regardless of severity, should be considered during treatment decision making.

Background

Asthma and chronic obstructive pulmonary disease (COPD) are chronic inflammatory airways diseases that result in limitations of lung airflow [1,2]. The underlying disease mechanisms, however, differ markedly; asthma is considered a largely eosinophilic response, while COPD has typically been thought to be predominantly neutrophilic [3], although eosinophilic airway inflammation is now recognised in a subset of COPD patients [4,5].

Global Initiative for Asthma (GINA) guidelines recommend the use of blood EOS counts to identify patients who are most at risk of asthma exacerbations, and who are most likely to benefit from anti-interleukin 5 (IL5)-containing treatment regimens [2]. Blood EOS count has been reported as a useful predictive marker of response to anti-IL5 therapy in severe asthma [6], and has also been used to direct anti-IL5 treatment in COPD clinical trials [7,8].

Blood EOS count has been proposed as a biomarker to direct corticosteroid therapy during COPD exacerbations [5] and to identify patients who will benefit from treatment regimens containing inhaled corticosteroids (ICS) [9–11], including those who may have had an exacerbation history [12]. Current Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend the use of blood EOS counts to identify patients with the greatest likelihood of treatment benefit with ICS [1].

Several challenges, however, are currently perceived to limit the application of blood EOS count as a biomarker in clinical practice. Different predictive cut-off points based on data from randomised controlled trials have been reported in asthma and COPD [13–17], and recent data suggest that blood EOS count is a continuous, rather than dichotomous, variable [18,19]. Little robust evidence exists to support the current understanding of what are considered 'normal' levels of blood EOS in different populations and conditions. Studies in healthy populations show a broad range of blood constituents, including EOS counts, with potential confounding from a variety of factors such as age, sex, atopy and environmental exposure [20–23]. While these factors may potentially influence normal blood EOS ranges, underlying inflammation in disease states also has an impact. As inflammation is predominantly eosinophilic in asthma and neutrophilic in COPD, this may result in a simple perception, but not one necessarily derived from evidence, that blood EOS levels are high in asthma and lower in COPD.

The clinical context for using blood EOS counts as a biomarker of treatment response in asthma and COPD therefore requires a better understanding of blood EOS distributions and ranges. We conducted a comprehensive literature review and meta-analysis to describe the absolute blood EOS count distribution among patients with chronic airways disease (asthma, severe asthma, COPD), non-disease (control) patients from these studies, and in general populations. Using these data, we also sought to describe blood EOS-associated factors.

Methods

Information sources and literature search strategy

A comprehensive literature search of the PubMed and EMBASE databases was performed to identify relevant articles published between 01 Jan 2008 and 12 Nov 2018. This comprehensive review followed the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [24] for systematic reviews except for two points: the review was not registered, and no formal assessment of the risk of bias or quality of the evidence for included studies was performed, however, this was informally assessed. Two separate search strategies were developed and implemented in both databases: the first search comprised key terms related to asthma, severe asthma, COPD and blood EOS; the second search consisted of key terms for general populations and blood EOS (Supplementary Table 1 shows PubMed example search strategies to identify articles reporting blood EOS data for [A] disease populations [asthma, COPD] and [B] general populations). We separated severe asthma from asthma because it is perceived that the severe asthma population has a higher blood EOS count and requires different management, as recommended in severe asthma treatment guidelines [2,25].

PubMed and EMBASE literature searches included English-language articles (full-text, articles in press, editorials and letters) that reported observational studies on asthma, severe asthma, COPD or general populations, and data on blood EOS (absolute cell count). Any case reports, case series, interventional clinical trials, randomised controlled trials, reviews and conference abstracts were excluded. Articles reporting results from predominantly paediatric-adolescent studies/populations; studies with a sample size <200; studies including hospitalised/intensive care unit samples only; studies where EOS count was used as part of study inclusion/exclusion criteria; and studies with no absolute EOS count information available were also excluded.

Articles were selected for inclusion in the review based on searches conducted by two independent reviewers. Firstly, both reviewers independently screened titles and abstracts of all English-language articles resulting from the searches (and relevant references cited in those articles) against the pre-defined inclusion and exclusion criteria. Secondly, the full texts of identified articles considered potentially eligible were screened against the inclusion and exclusion criteria. Discrepancies between the two reviewers were resolved through consensus discussion between the reviewers, or by contacting a third reviewer.

Data extraction

Data were independently extracted from articles included in the full-text review phase by both reviewers, with any discrepancies resolved by consensus or a third reviewer. Data extracted included study characteristics and details of the author and year of publication, country in which the study was conducted, study name, sample size, the definition of asthma/severe asthma or COPD used, and study inclusion/exclusion criteria. Within each study, data on participant characteristics, which included: age, proportion of males in the study, body mass index (BMI), smoking status, percentage predicted forced expiratory volume in 1 second (FEV_1), the FEV_1/forced vital capacity (FVC) ratio, ICS use, oral corticosteroid (OCS) use and selected comorbidities were extracted. Blood EOS data were extracted for study outcomes, including blood EOS counts, distributions and cut-off point data.

No formal assessment of the risk of bias or quality of the evidence for included studies was performed.

Data handling

Extracted data from source articles are presented according to population type: asthma, severe asthma, COPD, control populations (defined as non-asthma, non-COPD from the selected asthma and COPD studies), and general populations (as defined in each respective article).

Absolute blood EOS counts were converted to cells/μL if not originally reported as such. For included articles that reported blood EOS data only for sub-groups for mean, geometric mean or EOS categories, data were combined where possible to create a 'total population' that was used in the main part of the review. Such combination of data was feasible for results reported as mean, geometric mean or EOS categories, but not for results reported as medians. Combined estimates of number (n) and percentage for attributes were derived based on the number of patients for whom data were available and the agreed assumptions (Supplementary Methods).

Since this review was conceived, two relevant studies have recently been published, which are also discussed in context with our findings [26,23].

Meta-analysis

For each study included in the meta-analysis, the median and upper and lower quartile values were available (with the exception of the Mäkelä et al. study [54], for which 5th and 95th percentiles were available). These quantiles can be used to calculate the corresponding standard deviation (SD), provided that the variable under consideration is approximately normally distributed and especially that its distribution is approximately symmetrical. It was judged that these criteria would be more nearly met by transforming the quantile values to logarithms. The SD was then estimated as follows:

If Z is a standard normal variable and N = number of observations in study,

$$Z \sim N(0, 1)$$

then

$$\text{upper quartile}(Z) = 0.67448.$$

Hence if the log-transformed response variable in a study is

$$X \sim N(\mu, \sigma)$$

then

$$SD(X) = 1/0.67448 \times (\text{upper quartile}(X) - \mu)$$

$$= 1/0.67448 \times (\mu - \text{lower quartile}(X))$$

Using both upper and lower quartiles, this value is estimated by

$$SD(X) = 1/0.67448 \times$$

$$\sqrt{(((\text{upper quartile}(X) - \text{median}(X))^2 + (\text{median}(X) - \text{lower quartile}(X))^2)/2)}.$$

The standard error (SE) of the $\log_{10}(\text{median})$ was is calculated as

$$SE(\log_{10}(\text{median})) = SD(\log_{10}(\text{median}))/\sqrt{(N)}.$$

The values of $\log_{10}(\text{median})$ and $SE(\log_{10}(\text{median}))$ obtained by this method were used to perform a random-effects meta-analysis [27]. For the study by Mäkelä et al. [54], the same approach was used but applied to the 5th and 95th percentiles instead of the quartiles.

Results

Literature search findings

In total, 7260 articles were identified by PubMed (n=4385) and EMBASE (n=2875) literature searches. After removal of duplicates, 5770 unique records remained (Figure 1); screening the title and abstract of these articles identified 442 relevant articles. Full-text screening of relevant articles excluded a further 351 articles. The reasons for exclusion were: low sample size (n<200), interventional study design, including only hospitalised patients, having a low age restriction (typically with a age range of 10–35 years [28–32]), reporting blood EOS by percentage only, having EOS as an inclusion/exclusion criterion, reporting data only for a population not of interest, duplicate articles, articles with a discrepancy, articles containing no relevant data or the data having been presented elsewhere. Thus, leaving a total of 91 identified publications for inclusion in the literature review: an asthma population (n=44); a severe asthma population (n=14); a COPD population (n=23); articles that included control populations without asthma or COPD (n=9); and articles in general populations (n=16). Some articles reported data for multiple populations.

Out of 91 publications, 5 studies in asthma [33–37], 2 studies in severe asthma [38,39], 2 studies in control populations without asthma or COPD [35,40], and 2 studies in general populations [41,42] only reported median EOS count data from sub-groups and not the total population; which therefore could not be combined to create total population-level data for these categories (sub-group data are thus presented separately: Supplementary Results B). Total population-level data were available for the COPD and control populations, respectively, for 2 of these studies however [33,40]. Details for the eligible articles, including study inclusion criteria, for which total population data could be calculated based on available data are reported in Supplementary Table 2 and an in-depth description of the studies is provided in the Supplementary Results A.

Briefly, the identified studies were conducted across the world. Of the 83 articles with available total population-level data, study populations were mainly in Europe (n=37 studies/n=46 populations), North America (n=20 studies/n=23 populations) and Asia (n=18 studies/n=18 populations), with 1 study (n=2 populations) in South America, 2 studies in Oceania and 3 studies in Africa; 2 studies included more than one region [71,78] and 14 studies included multiple populations [40,43,45,46,48,53,57,61,71,72,73,84,87,108]. Sample sizes ranged from as few as 200 to as many as 363,558 participants (asthma population); 22 studies included children (n=18, asthma; n=4, severe asthma [1 asthma study also reported a severe asthma cohort [43]]; n=1, control), while others were restricted to adults only. Spirometry, physician report and diagnostic codes from electronic medical

records were used to define asthma, severe asthma and COPD. Self-reported disease was a feature of 7 asthma studies [40,44–49]; diagnoses were confirmed using lung function testing as stated in 23 asthma studies [40–41,44–48,50–64], 8 severe asthma studies [43,53,57,61,65–68] and 18 COPD studies [40,69–87].

Population characteristics

Characteristics for the participants in analysed studies where total population-level data were available are reported in Table 1a–d.

Asthma

The range across the 39 asthma studies (Table 1a) for average age was 26.3–60.2 years; 23.0–60.6% were males. Across the studies the range of average FEV_1 was 74.5–102.1% of predicted and the range of FEV_1/FVC ratios was 0.68–0.93; 2 studies specifically included 'mild–moderate' asthma [53,79], 2 studies included 'mild–severe' asthma [57,94], 1 study included 'moderate–severe' asthma [89], 1 study included 'non-severe' asthma [43] and other studies did not define the included asthma severity. OCS use was reported in 13 studies by 0.5–60.3% of participants; 18 studies reported ICS use by 8.0–100% of participants. The most commonly reported comorbidities were allergic rhinitis/hay fever (10 studies, 11 populations; 2 cohorts in 1 study [61]) and a history of atopy/eczema (16 studies).

Severe Asthma

In the 12 severe asthma studies (Table 1b), the range of average participant age was 43–57.8 years with 19–43% males. The range of average FEV_1 was 66–78.9% and of average FEV_1/FVC ratios was 0.63–0.87. Nine studies reported OCS use by 8–64% of participants; 9 studies reported ICS use between 25–100% of participants. Recently approved biologic therapies were in use for severe asthma: anti-IgE in 6 studies (2.5%–64.1% of participants [57,66,67,101,103,105]) and anti-IL5 in 1 study (11.2% of participants [103]), while undefined 'specific immunotherapy' was reported by 2 studies (0.6–4.1% of participants [66,101]). The most commonly reported comorbidities for severe asthma were nasal polyps (9 studies), a history of atopy (7 studies) and allergic rhinitis (7 studies).

COPD

For the 23 COPD studies (Table 1c), the range of average age was 54.1–75.0 years and 37.4–97.3% of participants were male. The range of average predicted FEV_1 was 31–81% with FEV_1/FVC ratios of

0.45–0.67. Three studies reported use of OCS by 2–38.1% of participants; 17 studies reported ICS use by 7–89% of participants. Asthma history (7 studies) and diabetes were the most commonly reported comorbidities (6 studies).

Control and General Populations

The control populations (without asthma in asthma studies or COPD in COPD studies) from 7 studies (Table 1d) had a range of average ages of 46.6–71.1 years; 45–58.2% were males. The range of average predicted FEV_1 was 95–107%; the average FEV_1/FVC ratio was reported by 2 studies (0.78 in both). Five studies reported ICS use (3 studies reported ICS use by 1.4–3.5% of the asthma/COPD control populations [46,48,108]; 1 COPD study reported ICS use by 9.3% of the control population [72] and 1 asthma study reported ICS use by 27.4% of the control population [33]). In these studies, asthma history was reported in 10.2% and 7.6% of the control population respectively [33,72]. None reported OCS use and the most commonly reported comorbidities were allergic rhinitis/hay fever (2 studies) and asthma history (3 studies).

The 14 general population studies (Table 1d) had a range of average ages of 28–58 years; 33–59% of participants were males (1 study reported 33% males [117], the other studies ranged from 45–59% male). The range of average predicted FEV_1 was 96–107%, where available (5 studies), and the range of FEV_1/FVC ratios was 0.77–0.97 (5 studies). ICS use was reported by 2 studies (by 1.1–5% of participants [87,116]) and 1 reported ICS or OCS use in the last 2 days (by 4% of participants [28]); the most frequently reported co-morbidities were current asthma (5 studies) and allergic rhinitis/hay fever (2 studies).

Distribution of blood EOS

Seven studies that describe the distribution of blood EOS counts were identified [40,46,72,78,83,84,86]; among these there were 11 populations, with a general trend demonstrating a right-skewed distribution profile. Representative data are reproduced in Figure 2 for asthma, COPD and control/general populations [84,46]. Each histogram represents the results of a single representative study. The highest blood EOS counts reached ≥1000 cells/µL in a small proportion of individuals with asthma [46] (Figure 2a), COPD [76,81,82,84] (Figure 2b) and control populations [40,46,72,78,84] (Figure 2c). No distribution data were reported for severe asthma during this review period.

In the control population with healthy lung function of a US population-based COPD cohort, approximately 28% and 35% of individuals, respectively, had blood EOS levels of up to 1.2% and 2.4% [84]. Blood EOS distributions for the entire Copenhagen General Population Study followed a similar trend to the control populations [46]. Although the corresponding percentage of blood EOS was not reported, correlation analyses found that blood EOS counts of 100, 150 and 300 cells/µL, respectively, were equivalent to approximately 1.3%, 1.9% and 3.8% of total white blood cells in the study population [72].

Overall, these data indicate that for asthma, COPD and control populations, blood EOS count distributions are right skewed and therefore it is important to take the median/geometric mean EOS count into consideration when interpreting these values.

Absolute blood EOS counts

Absolute blood EOS count data are shown in Supplementary Table 3 for studies where a total population was published (67 studies/69 populations) or an arithmetic/geometric mean for a total population could be calculated from published sub-group data (14 studies/14 populations). The median and geometric mean values are presented graphically in Figure 3. Arithmetic mean data were not included in the figure owing to the skewed blood EOS distribution as described above. Overall, while there were differences between some studies in how asthma and COPD were identified and in the characteristics of the patients studied, reported blood EOS data were generally similar across the individual studies within a population type and most studies reported blood EOS counts >150 cells/µL (solid vertical line, Figure 3) in asthma, severe asthma, and COPD. Very few studies reported a 75th percentile of blood EOS counts above the upper limit of normal levels, which is generally considered to be approximately 500 cells/µL (dashed vertical line, Figure 3) [122–124].

Asthma

Of the 34 asthma studies with data on absolute blood EOS counts, 20 reported median counts ranging from 157–298 cells/µL and 1 reported a geometric mean count of 215 cells/µL (13 studies reported arithmetic mean counts of 233–507.9 cells/µL; 1 study reported both median and arithmetic mean counts [102]). Four studies where >20% of the study population used OCS at baseline showed similar blood EOS counts (median: 200 cells/µL [89,99], geometric mean: 215 cells/µL [92] arithmetic mean: 263 cells/µL [93]). The meta-analysis of medians reported significant heterogeneity (τ^2 = 1951.2; degrees of freedom [df] = 17; p<0.001) and almost all variability was between studies rather than within studies (I^2 = 99.13%). The estimated median (95%

CI) count for the model was 207.1 (203.0–211.3) cells/μL. Three asthma studies reported the proportion of patients with blood EOS counts ≥150 cells/μL, ranging from 61.1–100% [73,93,125].

Severe Asthma

For severe asthma, 8 studies reported median blood EOS counts ranging from 200–400 cells/μL and no geometric mean data were reported (4 studies reported arithmetic means of 200–536.7 cells/μL; 1 study reported both median and arithmetic mean counts [105]). All studies reported data from the total severe asthma population, except for one study that reported median (interquartile range [IQR]) values of 240 cells/μL (130–460) for GINA category 4 and 280 cells/μL (100–540) for GINA category 5 [57]. The meta-analysis of medians reported significant heterogeneity (χ^2 = 345.4; df = 4; p<0.001) and almost all variability was between studies rather than within studies (I^2 = 98.84%). The estimated median (95% CI) count for the model was 285.7 (234.8–347.8) cells/μL. One severe asthma study reported the proportion of patients with blood EOS counts ≥150 cells/μL: 79.8% [103].

COPD

In COPD, 6 studies reported median counts ranging from 150–183.5 cells/μL and 1 reported a geometric mean count of 196.6 cells/μL [72] (11 studies reported arithmetic mean counts of 189.9–297.6 cells/μL). The meta-analysis of medians reported significant heterogeneity (χ^2 = 153.8; df = 5; p <0.001) and almost all variability was between studies rather than within studies (I^2 = 96.75%). The estimated median (95% CI) count for the model was 171.0 (159.1–183.9) cells/μL. Five COPD studies reported the proportion of patients with blood EOS counts ≥150 cells/μL, ranging from 18–72.7% [72,73,75,76,107].

Control and General Populations

Of the 6 studies with a control population (without asthma or COPD depending on the study) that included data on absolute blood EOS counts, 3 reported median counts between 100–160 cells/μL and 1 reported a geometric mean count of 182.1 cells/μL [72] (2 studies reported arithmetic mean counts of 149 and 210 cells/μL).

In the 13 general population studies with data on absolute blood EOS counts, 6 reported median counts generally below 150 cells/μL, although 1 large study was above this threshold at 170 cells/μL [87], and the National Health and Nutrition Examination Survey's general population recorded a median count of 200 cells/μL [28]. One study reported a geometric mean count of 163 cells/μL (7 studies reported arithmetic mean counts of 124.7–200.6 cells/μL).

The meta-analysis of medians reported significant heterogeneity (χ^2 = 440.2; df = 2; p <0.001) and almost all variability was between studies rather than within studies (I^2 = 99.55%). The estimated median (95% CI) count for the model was 157.0 (151.6–162.5) cells/µL.

Factors associated with blood EOS count

Çolak et al. [40] reported that the following factors were associated with a blood EOS count ≥300 cells/µL: age (per 10 years higher); sex (males versus females); BMI (per 10 kg/m^2 higher); smoking history (per 10 pack-years higher); allergy; use of airway medication; percentage predicted FEV$_1$ below 80% and/or lower limit of normal (LLN); FEV$_1$/FVC ratio below 0.70 and/or LLN [40]. These factors are illustrated in Figure 4a. Conversely, familial predisposition of COPD was associated with a lower blood EOS count [40]. However, since this review was conceived and completed, two further relevant studies have been published [23,26], although it should be noted that these studies did not use a cut-off of ≥300 cells/µL for defining higher blood EOS counts. The Lung, hEart, sociAl, boDy (LEAD) study, a large Austrian general population study of 11,042 participants, found younger age (≤18 years), male sex, spirometric diagnosis of asthma, current smoking (but not cumulative former smoking ≥20 pack years), positive skin prick test (SPT), spirometric COPD diagnosis, presence of metabolic syndrome and adiposity were all significantly associated with higher EOS ≥210 cells/µL from multivariable analyses with a cut-off point determined using the 75th percentile of LEAD study data [23] (Figure 4b and c). Diabetes, hypertension and cardiovascular disease were not associated with high EOS counts in this large general population sample [23]. Also, increasing numbers of concomitant associated factors was associated with higher EOS counts [23]. The analysis from the Program for Control of Asthma in Bahia (ProAR) study, conducted in Brazilian patients with non-asthmatic controls (n=454) found that positive SPT, elevated total IgE, comorbid allergic rhinitis and being a current smoker were all associated with having higher blood EOS counts [26] (Figure 4d and e). This study did not use a specific threshold for defining "higher blood EOS count" but instead identified which patient subgroups had significantly different median counts; the highest of these subgroup medians was 252 cells/µL (for current smokers) [26]. When analysed in a stratified manner, having none of these four identified risk factors was associated with a median blood EOS count of 106 cells/µL, increasing to 153 cells/µL with one risk factor, and further increasing to 190–192 cells/µL with 2–4 risk factors [26]. Overall, these data suggest that an individualised approach based on personal medical and lifestyle history may be important when interpreting blood EOS counts.

Discussion

This comprehensive literature review included 91 observational studies that reported baseline EOS counts in asthma, severe asthma, COPD, control (non-asthma/COPD) and general populations. Despite the wide range of treatment options available for asthma and COPD, a substantial unmet clinical need remains. Advances in therapy have been hampered by the heterogeneity within these conditions, and a different approach is required to provide effective care to patients at an individual level. The ability to predict treatment response in patients is crucial to tailoring individualised therapy and blood EOS count has emerged as a candidate biomarker in both asthma and COPD. However, there is uncertainty in the current understanding of blood EOS counts, including what constitutes a 'normal' count and what factors influence EOS levels. To better characterise blood EOS in health and disease, we conducted a study of the published literature to collate and describe absolute blood EOS count data reported for patients with asthma, severe asthma and COPD, as well as participants in control and general populations. Where median (IQR) EOS values were provided, a random-effects meta-analysis was conducted to investigate the degree of variability between and within studies. Meta-analyses in medical research provide additional information about the strength of available data surrounding a disease and therapy area. Our meta-analysis indicated that variability was much more common between studies rather than within studies.

Ninety-one publications were included in the literature review, covering patient, control and general populations; sample sizes ranged from 200–363,558 participants. The distribution of EOS values in these studies were non-normally distributed and clearly right skewed, demonstrating the need for careful interpretation of EOS data and supporting the use of median or geometric means in analyses. Limited information is available on what constitutes a 'normal' range for blood EOS levels and this remains an area of uncertainty in urgent need of clarification. Generally, 5th–95th percentile denotes a normal range, however given the skewed distribution of EOS count data, IQR (25th–75th percentile) is the most relevant measure for understanding EOS reference ranges to avoid influence by outliers. The LEAD study reported 70–180 cells/μL and 30–395 cells/μL for IQR and 5th–95th percentile respectively, demonstrating a smaller number of the population distributed in the upper quartile [23]. This finding was more obvious in the ProAR study as the IQR was 96–252 cells/μL and 5th–95th percentile was 50–508 cells/μL [26].

The right-skewed nature of EOS distributions was particularly relevant for the studies in control and general populations we identified, where only 6 studies, of which 3 reported IQR, and none reported 95% CI. For instance, one general population study reported a blood EOS range of 0–8400 cells/μL

[28]. Furthermore, many studies reported arithmetic mean EOS counts and were, therefore, difficult to interpret. Nonetheless, control populations, demographically representative of the study group but without asthma or COPD, as appropriate, reported median/geometric mean blood EOS counts ranging from 100–182 cells/µL. Similarly, studies examining general population cohorts reported median/geometric mean blood EOS counts ranging from 100–200 cells/µL. The meta-analysis for the 3 included studies (2 asthma control populations and 1 general population) reported a median (95% CI) of 157.0 (151.6-162.5) cells/µL. Importantly, the level of blood EOS is naturally bound to sex and age as shown recently by the LEAD general population study, covering an age range from 6–>80 years [23]. The LEAD study reported that EOS counts are highest in infancy and adolescence, independent of age in adults (≥18 years) and observed at higher levels in males in all age ranges [23]. This has been reflected in higher reference values for children in many countries [126,127], but may not be recognised in clinical studies. As expected, the range of reported mean ages was higher in COPD cohorts (54.1–75 years) than for asthma/severe asthma (26.3–60.2 years).

Although 18 of the identified asthma studies permitted inclusion of participants under the age of 18, only 2 studies reported age ranges that included <18 years old (14–102 [96]; 16–85 [101]). A median blood EOS count was only available for the latter of these studies, 188 cells/µL [101]; lower than the median counts ≥200 cells/µL reported by most (n=17) asthma studies reporting median/geometric mean blood EOS data (n=22). The meta-analysis for the 18 included studies reported a median (95% CI) of 207.1 (203.0-211.3) cells/µL. Of the 9 asthma studies that had a higher proportion of males than females, 4 reported median/geometric mean blood EOS counts (165–298 cells/µL [44,48,51,60]); the range of median/geometric mean counts in the other asthma studies was similar (157–280 cells/µL). All severe asthma studies had a higher proportion of females than males and reported median EOS counts >200 cells/µL. The meta-analysis of the 5 eligible severe asthma studies reported a median (95% CI) of 285.7 (234.8-347.7) cells/µL; the highest estimate calculated among the meta-analyses. For COPD studies (n=23), all median blood EOS levels were ≥150 cells/µL and <200 cells/µL; 2 of the 23 COPD studies had a higher proportion of females than males [107,109], however neither of these reported median/geometric mean blood EOS counts precluding any interpretation of sex on EOS levels. For the 6 eligible COPD studies, a median (95% CI) of 171.0 (159.1-183.9) cells/µL was reported.

In terms of ethnicity, existing studies report higher blood EOS counts in White and Hispanic populations versus Black and non-Hispanic populations [128,129]. There are limited studies into the difference in EOS count between Asian and other ethnicities, typically reporting similar blood EOS

levels across Asian and European populations [130]. In our review, obtaining data from Asian countries was difficult due to the limited number of studies. For asthma, 2 studies were conducted in India [52,60], 3 in Korea [41,56,63] and 2 in Japan [64,92]. There were no severe asthma populations from Asia in this review. For the COPD studies, 3 were from Korea [74,81,83] and 3 were from Japan [82,85,86]. For the general population analysis, 1 study was carried out in Japan [117], 1 in Thailand [114] and 1 in China [119]. It was not possible to analyse the ethnicity breakdown in each study for this review as the data were not available, however this may be an interesting avenue of future investigation.

A blood EOS cut-point of 150 cells/μL, equivalent to ~2% of circulating white blood cells, has been used to direct anti-IL5 therapy in severe asthma [6] and predict ICS responsiveness in COPD [9–12]. At least half of patients had levels above this threshold in asthma, severe asthma and most COPD studies reporting the proportion of patients with blood EOS counts ≥150 cells/μL [72,73,93,103,107,125], indicating that a substantial proportion of patients may benefit from these therapies. The number of studies included, and their sample sizes, provides weight to the strength of the evidence presented here. Within and between populations there was variation in EOS levels, partly contributed by difference in study populations, reflecting that there is a continuum of EOS counts and not necessarily an 'ideal' cut-off related to health and disease. Additionally, blood EOS count can potentially be used as a biomarker for response to systemic corticosteroid use in the treatment of COPD [5,11]. More recently, Sivapalan et al. demonstrated non-inferiority (versus standard of care) in treating patients with severe COPD in hospital through eosinophil-guided corticosteroid therapy (i.e. patient received subsequent dose of corticosteroid treatment if blood EOS count was ≥300 cells/μL) [131].

There is increasing evidence that EOS levels are linked to disease outcomes and treatment response. For example, higher EOS counts have been associated with increased risk of future exacerbations and improved response to treatment with ICS in patients with COPD and a history of exacerbations [132,133]. Similarly, in asthma, exacerbations are more frequent in patients with high counts (>400 cells/μL) than those with counts below this threshold [95,96], however the use of blood EOS counts as a predictor of severity and outcomes has been more controversial due to varied study designs and EOS cut-offs [133]. That EOS counts are such a variable measure influenced by medical conditions and treatment, yet could be predictive of disease outcomes, illustrates the need for their use in the context of clinical status to determine the best interventions to use on a case-by-case basis.

Sparse information is available on factors influencing blood EOS levels and two studies have investigated this since our 2008–2018 data extraction was undertaken [23,26]. These studies found a variety of factors to be associated with an increased blood EOS count in healthy individuals, such as young age (<18 years), male gender, current smoking, elevated IgE and positive SPT [23,26], plus adiposity and metabolic syndrome in total populations. Findings from an earlier study of a healthy population showed that the upper limit of the blood EOS range is higher in patients with a history of allergy compared to those without allergy [134]. Smoking is thought to be a potential confounder for blood EOS count in COPD [1], however Pedersen et al. recently reported that tobacco consumption was not causally associated with EOS in their analysis designed to compare blood cell count in current (n=17,852) and former (n=41,759) smokers with never smokers (n=44,996) using a Mandelian randomisation approach in the Copenhagen General Population Study [135]. Additionally, with regards to the link between obesity and blood EOS count, Peerboom et al. did not find an association between BMI and blood EOS count in a cohort of 1217 patients with asthma [136]. More recently, Esteban-Gorgojo et al. reported a close link between children and adolescents with asthma and the following conditions: concomitant food allergies; sensitisation to pollen and lipid transfer protein; growth alterations and high EOS count (N=815) [137]. They also suggest stratifying data by sex in future studies due to observable differences in certain characteristics between males and females [137]. Risk of elevated EOS count is also reportedly higher in patients with asthma versus those with COPD [23], however, we are not aware of other studies investigating factors influencing EOS counts in asthma or COPD patient populations specifically and this represents a significant gap in our knowledge of EOS in airway disease. More information is needed to highlight the aspects of a patient's medical history that should be considered when making treatment decisions based partly on blood EOS levels. In accordance with our findings, recent studies have shown variability in blood EOS counts with multiple influencing factors that suggest this measure exists along a continuum and that considering these as a dichotomous variable with a single cut-off point for clinical use is overly simplistic [138].

This comprehensive literature review combined data from various sub-populations where studies did not report a total population. This method allowed for comparisons between studies based on total populations, but may have been a limitation of the study as the estimates for the combined populations were only estimates calculated on the available data; however, the strength of the number of studies included, and the total number of patients from whom data was utilised, adds weight to the conclusions of this review and reduces the likelihood that extraneous estimates could have adversely affected the outcomes of our analyses. A further possible limitation was that studies

were only included if they reported absolute EOS count, which excluded those reporting only percent EOS and limited the pool of studies. Unfortunately, it was not possible to interconvert units between absolute EOS count values into percentages of total white blood cells and vice versa as the original raw data were not available, so comparable data could not be shown for certain studies, e.g. those illustrated in Figure 2a and c [46] versus 2b and d [84]. Additionally, it was not possible to evaluate studies by medication use due to lack of access to the full datasets for each study. While the percentages of patients receiving OCS were reported in the original publications, the corresponding EOS counts for these individuals were not available for all studies included in this review. In future studies it would be of value to investigate EOS counts in patients according to treatment type, including biological therapies. It should be noted that the inclusion of studies from countries across the world contributed to the broad range of median values observed, and, for example, the possibility of classic endemic eosinophilic infections such as with parasites was not routinely evaluated/reported. Several articles were excluded despite meeting the inclusion criteria as they included duplicate cohorts with other studies [139], described very specific populations (e.g., male firefighters in New York at the time of 9/11 [140]), or categorised subgroups according to patients' EOS levels (e.g., 'severe uncontrolled eosinophilic asthma' [88]). Among studies that were included in the review, the use of different entry criteria for individual studies within a population category may possibly have influenced the reported ranges of EOS levels but we were not able to control for or formally assess this.

Few of the articles included gave information regarding the impact of medication on blood EOS count which prohibited the inclusion of this as part of the study. In severe asthma, 6 studies reported that a proportion of patients were receiving biologic therapies (anti-IgE, anti-IL5, or undisclosed 'specific immunotherapy') [57,66,67,101,103,107], which may have influenced their blood EOS counts, although the median counts in these studies (200–300 cells/µL) were within the overall range of median counts reported in severe asthma (200–400 cells/µL). Similarly, while OCS use may have influenced blood EOS counts, in studies reporting any OCS use by >15% of participants the median/geometric mean counts in asthma (200–215 cells/µL [89,92,99]) and severe asthma (228–300 cells/µL [43,66,67,68]) were within the reported overall ranges of median/geometric means in asthma (157–298 cells/µL) and severe asthma (200–400 cells/µL).

The main strengths of this study lie in the inclusion of key target disease populations (asthma, severe asthma and COPD) for eosinophilic treatment response, together with control and general populations, providing a greater overview of EOS levels in disease and the shortcomings of

comparability between them for the first time. The number and power of the studies included additionally strengthens the evidence provided in this comprehensive literature review.

Based on reported median/geometric mean levels, blood EOS counts were highest in severe asthma and outside the median ranges for control and general populations. While lower than for severe asthma, the blood EOS count range in asthma was generally higher than, and the range in COPD within, the observed ranges for control and general populations. The observation that blood EOS count was right skewed emphasises the importance of conducting analyses based not on arithmetic means but on median/geometric mean values. Our findings confirm that variation in blood EOS counts is evident within and between asthma and COPD populations, associated control populations, and in general populations. General population studies can reveal the underlying associations of blood EOS levels with factors such as age, sex and comorbidities, and studies in conditions such as asthma and COPD thus need to be considered in this context. Moreover, the potential modulation of EOS levels by medical history, i.e., accounting for treatment effects, has to be considered if EOS levels are to be used in personalised medicine. The variability of blood EOS counts derived from the different patient cohorts support the need for a personalised approach that considers all these potential influencing factors in the patient's medical history when interpreting blood EOS count.

Author Contributions

All authors were involved in the study design and in data interpretation, provided critical review of the manuscript drafts during development and approved the final draft for publication.

Competing Interests

VSB, NB, MKVD, NG and NK report employment by GlaxoSmithKline and GlaxoSmithKline stock/share ownership. SH reports unrestricted grants from Astra Zeneca, GlaxoSmithKline, Böhringer Ingelheim, Menarini, Chiesi Farma, Pfizer, MSD, Air Liquide, Vivisol for the Ludwig Boltzmann Research Institute of Lung Health supporting the LEAD study.

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Figure legends
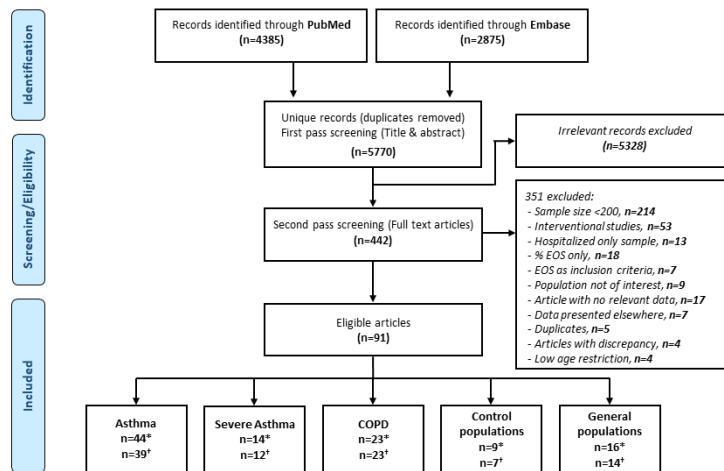
Figure 1. PRISMA diagram of articles for inclusion, overall and by population type

*The sum across the five categories (n=107) is greater than n=91 because some articles reported data for multiple relevant populations
†Studies where total population-level data were available, data for the studies presenting subgroup-level only data are presented in Supplementary Results B.
Abbreviations: COPD, chronic obstructive pulmonary disease; EOS, eosinophil; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses
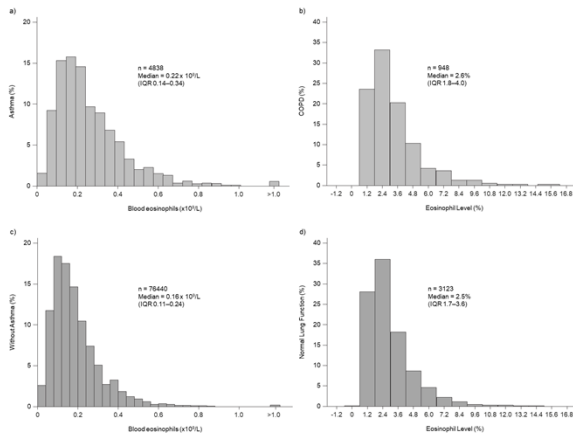
Figure 2. Blood EOS distributions in asthma (a), COPD (b), and control (c)/general populations (d)

[b) and d) Adapted, with permission, from: DiSantostefano RL, Hinds D, Le HV et.al. Relationship between blood eosinophils and clinical characteristics in a cross-sectional study of a US population-based COPD cohort. Respir Med. 2016 Mar;112:88-96] [84]
Abbreviations: COPD, chronic obstructive pulmonary disease; EOS, eosinophil

a) Asthma studies

Study	N	Median (IQR)[range]
Calciano L (2018) GEIRD	287	165.2 (99.5–261.0)
Çolak Y (2018) CGPS	449	160 (110–270)
Kerkhof M (2018) CPRD and OPCRD	363,558	200 (110–350)
Lima-Matos A (2018)	452	235 (131–399)
Papi A (2018)	7195	200 (120–320)[#]
Makela MJ (2018)[a]	4357	270.0 (50.0–1040.0)
Teague WG (2018) SARP II	213	189 (111–320)
Pretolani M (2017) COBRA	1080	230 (120–440)
Vedel-Krogh S (2017) CGPS	4838	220 (140–340)
de Groot JC (2016)	491	200 (100–300)
Price D (2016)	130,547	200 (120–350)
Tuomisto LE (2016) SAAS	203	280 (150–420)
Price DB (2015)	130,248	200 (120–340)
Westerhof GA (2015)	336	200 (100–300)
Agarwal R (2014)	296	298 (174.5–500)
Schleich FN (2014) Retrospective cohort	508	230 [0–3220]
Schleich FN (2014) Prospective cohort[b]	250	188 [10–1133]
Tran TN (2014) NHANES	1721	157 (75–267)
Amelink M (2013)	200	200 (100–340)
Bouzigon E (2012) EGEA	494	200 (140–320)
		gmean (95%CI)
Akiki Z (2017) EGEA II	283	215 (140, 320)

b) Severe asthma studies

Study	N	Median (IQR)[range]
Haughney J (2018)[c]	884	400 (200–700)
Lima-Matos A (2018)	544	248 (141–384)
Maio S (2018) RItA	493	300.0 (170.0–495.0)
Teague WG (2018) SARP III	313	228 (134–399)
Chipps BE (2017) TENOR II	341	200 (200)*
Chaudhuri R (2016)	1042	280 (110–540)
Newby C (2014) BTS Refractory SA cohort	349	300 (490)*
Schleich F (2014) BSAR	350	240 [0–3144]

c) COPD studies

Study	N	Median (IQR)
Çolak Y (2018) CGPS	404	180 (120–260)
Acartürk Tuncay E (2017)	1066	150 (90–230)
Kim SW (2017) KOLD	307	183.5 (111.5–316.5)
Song JH (2017) KOCOSS	467	166.5 (89.6–272.8)
Vedel-Krogh S (2016) CGPS	7225	180 (120–270)
Suzuki M (2016) Hokkaido COPD Cohort Study	268	169 (94–261)
		gmean (95%CI)
Landis S (2018) CPRD	27,557	196.6 (195.1, 198.3)

d) Controls (non-asthma, non-COPD) and *General Population studies*

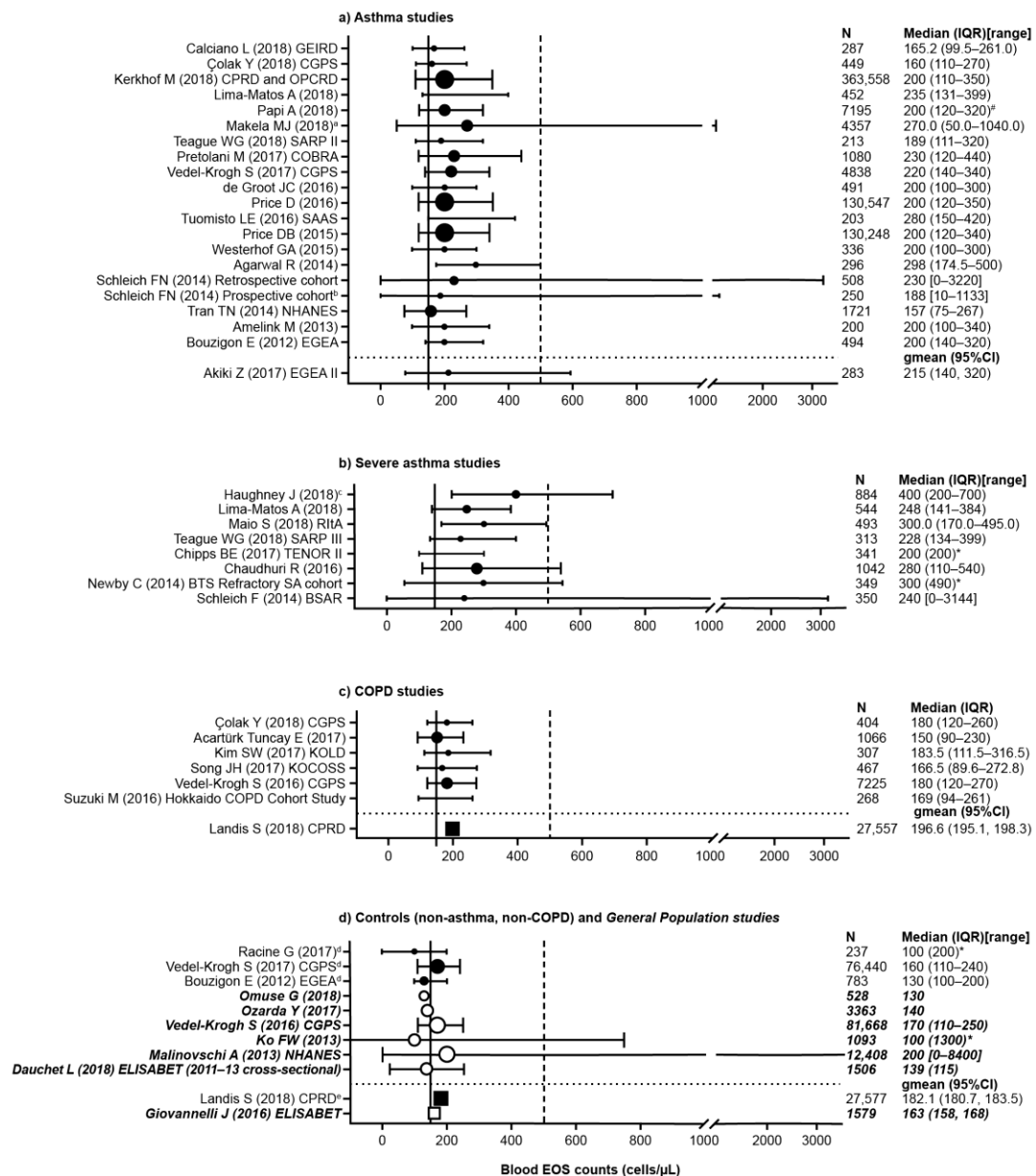| Study	N	Median (IQR)[range]
Racine G (2017)[d]	237	100 (200)*
Vedel-Krogh S (2017) CGPS[d]	76,440	160 (110–240)
Bouzigon E (2012) EGEA[d]	783	130 (100–200)
Omuse G (2018)	*528*	*130*
Ozarda Y (2017)	*3363*	*140*
Vedel-Krogh S (2016) CGPS	*81,668*	*170 (110–250)*
Ko FW (2013)	*1093*	*100 (1300)**
Malinovschi A (2013) NHANES	*12,408*	*200 [0–8400]*
Dauchet L (2018) ELISABET (2011–13 cross-sectional)	*1506*	*139 (115)*
		gmean (95%CI)
Landis S (2018) CPRD[e]	27,577	182.1 (180.7, 183.5)
Giovannelli J (2016) ELISABET	*1579*	*163 (158, 168)*

Blood EOS counts (cells/µL)

Figure 3. Forest plots of median (IQR) and geometric mean (95% CI) blood EOS counts for each of the five population types: (a) asthma, (b) severe asthma, (c) COPD, (d) controls and *general populations*

Median (IQR) depicted as circles. Geometric mean (95% CI) depicted as squares. In 'Controls (non-asthma, non-COPD) and *General Population studies*' (d), shaded symbols indicate the control populations while General population studies are shown with text in italics and using white symbols for plotted median/geometric mean values. Symbols are presented according to study size: 2pt, N<500; 4pt, N=≥500–<1000; 6pt, N=≥1000–<10,000; 8pt, N=≥10,000–<100,000; 10pt, N>100,000. Horizontal dotted lines represent the division between studies presenting median and geometric mean data. Vertical solid lines indicate a blood EOS count of 150 cells/µL, while dashed lines represent the upper limit of normal blood EOS levels, generally considered to be approximately 500 cells/µL [120–122].

Unless otherwise indicated all studies measured the blood EOS values at baseline. *Where IQR was reported as one value, the range could not be plotted due to unknown skew. [#]5-95%iles, not IQR or range.

[a]Blood EOS values not measured at baseline but during the observation period (Jan 2003–Aug 2013); [b]Data from a separate patient cohort (as indicated); [c]Maximum count in two years prior to index date; [d]Control population reported in the respective published study of asthma; [e]Control population reported in the respective published study of COPD.

Abbreviations: CGPS, Copenhagen General Population Study; CI, confidence interval; BSAR, Belgian Severe Asthma Registry; BTS, British Thoracic Society; COBRA, COhort of BRonchial obstruction and Asthma; COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; EGEA, Epidemiological study on the Genetics and Environment of Asthma; ELISABET, Enquête Littoral Souffle Air Biologie Environnement survey; EOS, eosinophil; GEIRD, Gene Environment Interactions in Respiratory Diseases; gmean, geometric mean; IQR, interquartile range; KOCOSS, Korean COPD Subtype Study; KOLD, Korean Obstructive Lung Disease; Nagahama, Nagahama Prospective Genome Cohort for Comprehensive Human Bioscience; NHANES, National Health and Nutrition Examination Surveys; OPCRD, Optimum Patient Care Research Database; RItA (acronym from the Italian words standing for Italian Registry of SUA); SA, severe asthma; SAAS, Seinäjoki Adult Asthma Study; SANI, Severe Asthma Network in Italy; SARP, Severe Asthma Research Program; SPIROMICS,

Subpopulations and Intermediate Outcome Measures in COPD Study; TENOR, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens; UK, United Kingdom; USA, United States of America
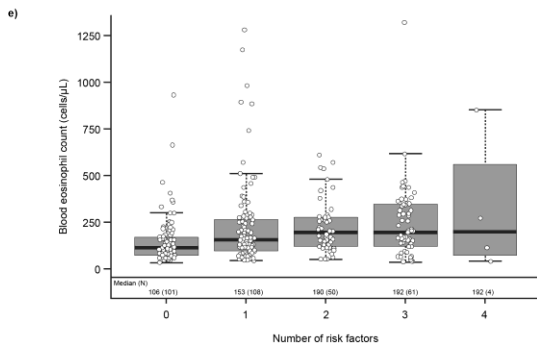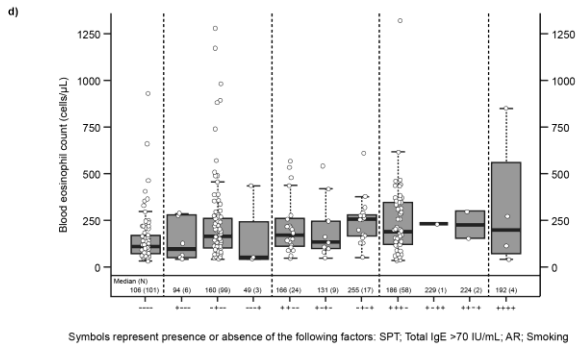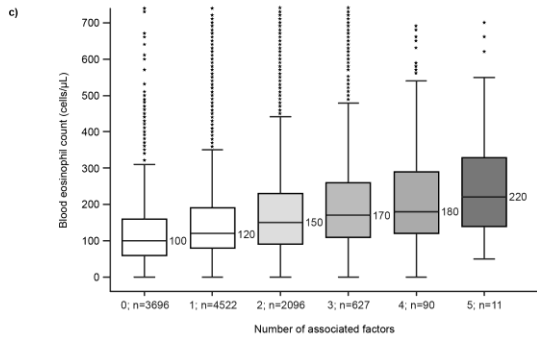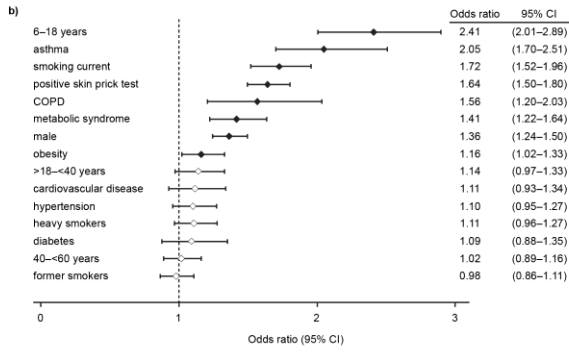
a)

	Blood eosinophil count ≥300 cells/µL	Odds ratio (95% CI)	p-value
	n		
Age (per 10 years higher)	751	1.09 (1.03–1.16)	0.005
Sex (males *versus* females)	751	1.41 (1.20–1.65)	2x10^{-5}
BMI (per 10 kg m^{-2} higher)	751	1.33 (1.12–1.58)	0.001
Current smoking	751	1.20 (0.96–1.50)	0.10
Smoking history (per 10 pack-years higher)	751	1.05 (1.01–1.10)	0.009
Familial predisposition to COPD	751	0.79 (0.63–0.99)	0.04
Familial predisposition to asthma	751	1.11 (0.89–1.40)	0.36
Familial predisposition to allergy	751	1.13 (0.91–1.40)	0.26
Childhood asthma or allergy	751	1.17 (0.97–1.42)	0.10
Allergy	751	1.26 (1.08–1.48)	0.004
Use of airway medication	751	2.03 (1.58–2.60)	3x10^{-8}
FEV$_1$ % pred <LLN	751	1.76 (1.43–2.17)	8x10^{-8}
FEV$_1$/FVC <LLN	751	1.33 (1.11–1.59)	0.002
FEV$_1$ <80% pred	751	1.60 (1.32–1.94)	2x10^{-6}
FEV$_1$/FVC <0.70	751	1.32 (1.11–1.56)	0.001
Postbronchodilator FEV$_1$/FVC <0.70	150	0.93 (0.64–1.37)	0.73
Reversibility	150	1.57 (0.99–2.48)	0.06

Odds ratio (95% CI)

0.1   1.0   7.0

b)

	Odds ratio	95% CI
6–18 years	2.41	(2.01–2.89)
asthma	2.05	(1.70–2.51)
smoking current	1.72	(1.52–1.96)
positive skin prick test	1.64	(1.50–1.80)
COPD	1.56	(1.20–2.03)
metabolic syndrome	1.41	(1.22–1.64)
male	1.36	(1.24–1.50)
obesity	1.16	(1.02–1.33)
>18–<40 years	1.14	(0.97–1.33)
cardiovascular disease	1.11	(0.93–1.34)
hypertension	1.10	(0.95–1.27)
heavy smokers	1.11	(0.96–1.27)
diabetes	1.09	(0.88–1.35)
40–<60 years	1.02	(0.89–1.16)
former smokers	0.98	(0.86–1.11)

Odds ratio (95% CI)

0   1   2   3

c)

Blood eosinophil count (cells/µL)

100, 120, 150, 170, 180, 220

Number of associated factors

0; n=3696   1; n=4522   2; n=2096   3; n=627   4; n=90   5; n=11

d)

Blood eosinophil count (cells/µL)

Median (N)															
106 (101)	94 (6)	160 (99)	49 (3)	166 (24)	131 (9)	255 (17)	186 (58)	229 (1)	224 (2)	192 (4)
----	+---	-+--	--+-	---+	++--	+-+-	+--+	-++-	-+-+	--++	+++-	++-+	+-++	-+++	++++

Symbols represent presence or absence of the following factors: SPT; Total IgE >70 IU/mL; AR; Smoking

e)

Blood eosinophil count (cells/µL)

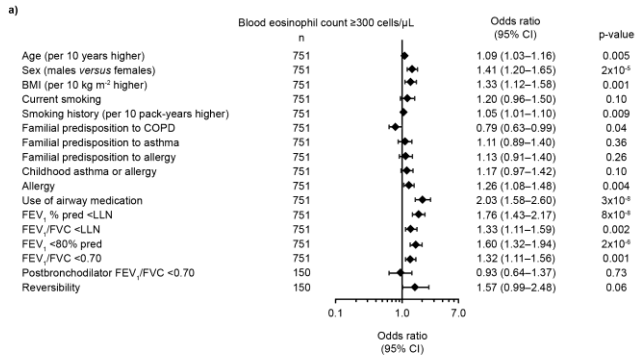| Median (N) | | | | |
| 106 (101) | 153 (108) | 190 (50) | 192 (61) | 192 (4) |

Number of risk factors

0   1   2   3   4

Figure 4. Blood EOS levels and risk factors of interest for the general population reported in (a) the Copenhagen General Population Study, (b, c) the LEAD study and (d, e) the non-asthmatic population reported in the ProAR study

[a) Reproduced with permission of the © ERS 2021 from: Çolak Y, Afzal S, Nordestgaard BG et al. Combined value of exhaled nitric oxide and blood eosinophils in chronic airway disease: the Copenhagen General Population Study. Eur Respir J. 2018;52(2):1800616] [40]
Clinical attributes associated with increased blood eosinophil count ($\geqslant$300 cells/µL). Reversibility was defined as forced expiratory volume in 1 second (FEV_1) reversibility of $\geqslant$12% and $\geqslant$200 mL. Logistic regression models were used. Estimates are unadjusted. p-values were from Wald's test.
[b) and c) Reproduced with permission of the © ERS 2021 from: Hartl S, Breyer MK, Burghuber OC et al. Blood eosinophil count in the general population: typical values and potential confounders. Eur Respir J. 2020;55(5):1901874] [23]
[d) and e] Reproduced with permission from Kwon N, Pizzichini E, Bansal AT et al. Factors that affect blood eosinophil counts in a non-asthmatic population: Post hoc analysis of data from Brazil. World Allergy Organ J. 2020;13(5):100119] [26]
Abbreviations: AR, allergic rhinitis; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; EOS, eosinophil; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LEAD, Lung, hEart, sociAl, body; LLN, lower limit of normal; ProAR, Program for Control of Asthma in Bahia; SPT, skin-prick test

TABLE 1a Patient/subject characteristics for total populations with asthma from included articles

Author (year), study or cohort name* [reference]	N	Age, years, mean ± SD or median (IQR)	Male, %	FEV₁ % predicted, mean ± SD or median (IQR)	ICS use, %‡	Co-morbidities, %§
ASTHMA (n=39 articles and n=40 populations)						
Amaral (2018) NHANES [50]	634	44.0 (31.0–57.0)	35.3	-	25	-
Calciano (2018) GEIRD [51]	287	42.5 ± 9.8	50.9	102.1 ± 14.6^{PreBD}		-
Çolak (2018) CGPS [40]	449	60 (51–70)	32	94 (85–104)	-	Allergy: 53
Kerkhof (2018) CPRD/OPCRD [88]	363,558	49.4 ± 20.6	35.9	-	82.8	CVD: 25.7; NP±CRS: 3.6; AR: 17.2; Atopy: 29.1
Kumar (2017) [52]	*463*	*26.3 ± 8.55*	*51.62*	*83.6 ± 17.99*	*-*	*-*
Lima-Matos (2018) [53]	452	35 (26–47)	23	87 (77–94)^{PostBD}	-	-
Llanos (2018) NHANES [73]	1609	37 ± 0.6	44	92.1 ± 0.6^{PreBD}	-	T1/2D: 6.8; CVD: 5.5
Mäkelä (2018) [54]	4357	59.78 (19.31–84.40 $^{[5–95th \%ile]}$)	31.71	-		COPD: 14.62; T1/2D: 14.44; CVD: 14.73
Papi (2018) [89]	7195	60.2 ± 15.1	34.4	-	-	AR: 19.9; Atopy: 27.2
Semprini (2018) [55]	212	50.5 ± 13.2	48.58	88.9 ± 19.8	74.1 (+LABA: 43.4)	-
Seo (2018) [56]	*323*	*48.2 ± 1.47*	*37.77*	*86.3 ± 1.48*	*-*	*Atopy: 42.41*
Teague (2018) SARP III [43]	213	44.5 ± 14.6	33.3	92.2 ± 15.5^{PostBD}	-	-
Akiki (2017) EGEA II [44]	283	36.6 ± 15.4	50.5	97.0 ± 16.8	50.7 [n=280]^{‡1}	AR: 62.9; Eczema: 46.8
Blakey (2017) [90]	118,981	45 ± 18	43	-	88	AR therapy: 31; Atopy: 4; Anxiety/depression: 5; NP±CRS: 3; AR diagnosis: 3
Burte (2017) EGEA [45]	*501*	*39.0 ± 16.45*	*52.69*	*97.4 (mean)*	*-*	*Atopy: 48.70*
Casciano (2017) [91]	*2701*	*45.0 ± 19.11*	*30.12*	*-*	*-*	*T1/2D: 11.3; CHF: 3.4; Malignancy: 3.0; Rheumatism: 1.6; Chronic lung disease: 1.6*
Kimura (2017) [92]	206	59.5 ± 13.8	40.3	95.4 ± 19.1$^{\parallel}$	-	Atopy: 68.0
Pretolani (2017) COBRA [57]	1080	49.1 ± 15.4	35.74	77.1 ± 22.9^{PreBD}; 80.6 ± 30.1^{PostBD}	92.3	CVD: 19.2; NP±CRS: 23.2; AR: 65.3; Atopy: 88.5; FA: 13.8
Vedel-Krogh (2017) CGPS [46]	4838	56 (47–66)	39	87 (73–98)	57	Allergy: 78
Zeiger (2017) [93]	9546	46.0 ± 12.7	38.3	-	85.3	AR: 30.2; Anxiety: 11.1; T1/2D: 11.0; Depression: 12.4; OSP: 3.1; Atopy: 2.0; Urticaria: 1.9; NP±CRS: 1.7
Casciano (2016) [94]	*1144*	*47 (mean)*	*29.16*	*-*		*T1/2D: 13.99; CVD: 5.94; Malignancy: 6.38*
de Groot (2016) [95]	491	51.8 ± 13.0	39.3	96.6 ± 18.2^{PostBD}	100^{‡2}	NP±CRS: 19.3; Atopy: 30.5
Nadif (2016) [47]	*716*	*41.6 ± 13.94*	*50.28*	*95.15 ± 19.38*	*48.32^{‡3}*	*-*
Tuomisto (2016) SAAS [58]	203	46 ± 14	41.9	88 (77–99)^{PostBD}	8.0 (at baseline) 76.4 (at follow-up)	-
Pola-Bibian (2016) [96]	831	57.3 (14–102 $^{[range]}$)	32.3	-	-	COPD: 13.7; CVD: 14
Price (2016) [97]	130,547	48.8 ± 17.4	34.1	-	-	T1/2D: 24.8; HF: 3.2; IHD: 6.0; AR: 44.2; Eczema: 32.3; Anxiety/Depression: 39.1
Price (2015) [98]	130,248	49 (36–63)	32.3	84 (71–96)	38.8$^{\#}$	T1/2D: 19.9; NP±CRS: 4.3; Atopy: 32.3; Allergy: 28.8
Westerhof (2015) [59]	336	53 ± 13	45	97 ± 18^{PostBD}	-	NP±CRS: 19; Atopy: 32
Agarwal (2014) [60]	296	36.2 ± 13.6	52.6	74.5 ± 4.03	-	Atopy: 27
Ali (2013) [62]	*1075*	*38.0 ± 15.63*	*60.56*	*86.04 ± 19.84*	*-*	*-*
Amelink (2013) [99]	200	53.9 ± 10.8	29.5	91.8 ± 20.9^{PostBD}	41.5	NP±CRS: 37; Atopy: 45
Hastie (2013) SARP [100]	*257*	*35.9 ± 12.86*	*27.63*	*80.08 ± 17.13^{PreBD}*	*-*	*-*
Lee (2014) [41]	*533*	*-*	*45.78*	*80.89 ± 1.35*	*-*	*-*
Park (2013) COREA [63]	*2067*	*49.7 ± 15.79*	*46.27*	*80.2 ± 21.44*	*-*	*-*
Schleich (2014) Retrospective [61]	508	52 (19–88)	39.56	84 ± 19	L/M/H: 14/27/28	NP±CRS: 22; AR: 58
Schleich (2014) Prospective [61]	250	50 (16–85)	39.6	82 ± 21	L/M/H: 14/25/28	NP±CRS: 27; AR: 56
Tran (2014) NHANES [102]	1721	40 ± 0.4†	37	-	-	-
Bouzigon (2012) EGEA [48]	494	39.8 ± 16.4	51	95.4 ± 19.0	17.6/48.4$^{Last 3/12 mo.}$	AR: 60.1
Matsunaga (2012) [64]	229	46.6 ± 14.7	41.92	96.7 ± 15.9	100.0	AR: 69.0; Atopy: 76.9
Nadif (2009) French EGEA [49]	381	36.5 ± 13.1	50.4	93.5 ± 19.9	52.2^{‡1}	-

*Entries in italic indicate publications for which data for the total population were calculated from the available published sub-group data (no data for the total population were originally reported)

†Mean ± SE

∥Maximum value from four different procedures

TABLE 1b Patient/subject characteristics for total populations with severe asthma from included articles

Author (year), study or cohort name* [reference]	N	Age, years, mean ± SD or median (IQR)	Male, %	FEV$_1$ % predicted, mean ± SD or median (IQR)	ICS use, %[‡]	Co-morbidities, %[§]
SEVERE ASTHMA (n=12 articles and n=12 populations)						
Haughney (2018) [65]	884	54.7 ± 15.9	31.3	-	24.9[‡1] (+LABA: 96.4[‡1])	COPD: 32.5; T1/2D: 13.9; CVD: 12.2; OSP: 4.3; Depression: 5.7; NP±CRS: 1.0
Heffler (2019) SANI [103]	437	54.1 ± 13.7	42.8	71.4 ± 20.2	100	Atopy: 70.7; Perennial AR: 62.2; NP±CRS: 42.6; AR: 44.6; FA: 8.7
Husereau (2018) [104]	212[‖]	43 ± 16	42	-	+LABA: 100[‡2]	T1/2D: 7; AR: 9; Atopy: 7; Anxiety: 9; Depression: 3
Lima-Matos (2018) [53]	544	52 (43–61)	19	70 (58–81)[PostBD]	38	-
Maio (2018) RItA [66]	493	53.8 ± 13.4 [n=483]	39.40	75.1 ± 20.5 [n=477]	97.1 (+LABA: 93.6) [n=488]	COPD: 11.8; Aspirin sensitivity: 22; NP±CRS: 30.2; AR: 62.4
Teague (2018) SARP III [43]	313	49.7 ± 12.8	32.9	77.9 ± 19.7[Max. postBD]	-	-
Chipps (2018) TENOR II [105]	341	57.8 ± 16.3	34.6	78.9 ± 20.6[‖1 PostBD]	84.0 (+LABA: 71.0)	COPD: 12.6; T1/2D: 0.6/15.5; CHF: 2.3; CAD: 5.6; OHD: 10.6; Aspirin sensitivity: 19.4; NP±CRS: 21.4; AR: 84.1; FA: 30.5; OSP: 15.8; Urticaria: 15.5; Malignancy: 9.7
Pretolani (2017) COBRA [57]	*613*	*51.1 ± 14.72*	*34.75*	*74.13 ± 33.00[PreBD]*	*98.84[‡3]*	*Atopy: 86.38; AR: 65.84; NP±CRS: 30.92; CVD: 20.59; FA: 14.80*
Zeiger (2017) [106]	261	52.1 ± 16.1	33.3	-	25.7 (+LABA: 87.0)	NP±CRS: 5.7; AR: 59.0; Atopy: 2.7; Anxiety: 17.2; Depression: 19.9
Chaudhuri (2016) [67]	1042	49.3 ± 14.1	34.7	71.0 (51.0–87.0) [n=947][PreBD]	100 [n=993]	Atopy: 75.1; Perennial AR: 35.7; NP±CRS: 13.8; CVD: 6.7; T1/2D: 4.3
Newby (2014) BTS Severe refractory Asthma [68]	349	45.80 ± 4.2 [n=349][†]	36.4	66 ± 24 [n=330][PreBD]	-	Atopy: 58.4; Perennial AR: 29.1; AR: 37.9; Eczema: 27.9; NP±CRS: 13.5
Schleich (2014) BSAR [101]	350	55 ± 0.8	43	68 ± 1.2	-	Atopy: 70; CRS: 49; Overweight: 47; GERD: 36; NP±CRS: 19; Depression: 19; Bronchiectasis: 16

*Entries in italic indicate publications for which data for the total population were calculated from the available published sub-group data (no data for the total population were originally reported)

[‖]EOS data available for n=212; [‖1] Global Lung Function Initiative estimates of percent predicted pre-BD and post-BD FEV

[†]Derived values

[‡]Data represent baseline values, unless otherwise indicated: [‡1]≥1 prescription 2 years prior to index date; [‡2]At index date; [‡3]Time of assessment not reported

[§]CVD excludes high blood pressure; atopy includes eczema; perennial AR includes perennial allergen sensitization

Abbreviations: AR, allergic rhinitis; BD, bronchodilator; BSAR, Belgian Severe Asthma Registry; BTS, British Thoracic Society; CAD, coronary artery disease; CHF, congestive heart failure; COBRA, COhort of BRonchial obstruction and Asthma; COPD, chronic obstructive pulmonary disease; CRS, chronic rhinosinusitis; CVD, cardiovascular disease; EOS, eosinophil; FA, food allergy; FEV$_1$, forced expiratory volume in 1 second; GERD, Gastrooesophageal reflux disease; ICS, inhaled corticosteroid; IQR, interquartile range (25th–75th percentile); LABA, long-acting β2-agonist; NP, nasal polyps; OHD, other heart disease; OSP, osteoporosis; RItA, The Italian severe/uncontrolled asthma registry; SANI, Severe Asthma Network in Italy; SARP, Severe Asthma Research Program; SD, standard deviation; TENOR, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens; T1/2D, type 1/2 diabetes

TABLE 1c Patient/subject characteristics for total populations with COPD from included articles

Author (year), study or cohort name* [reference]	N	Age, years, mean ± SD or median (IQR)	Male, %	FEV$_1$ % predicted, mean ± SD or median (IQR)	ICS use, %[‡]	Co-morbidities, %[§]
COPD (n=23 articles and n=24 populations)						
Chalmers (2018) [69]	*4009*	*67.8 ± 10.30*	*60.48*	*59.26 ± 19.00*	*43.53[‡1]*	*Asthma history: 15.33; T1/2D: 15.23; CVD: 10.08; OSP: 12.8*
Çolak (2018) CGPS [40]	404	68 (60–75)	54	81 (69–94)	-	Asthma history: 17; Allergy: 27
Greulich (2018) COSYCONET [70]	334	64.37 ± 8.33	63.2	55.5 ± 17.97	57.8	Asthma history: 20.1
Halper-Stromberg (2018) COPDGene [71]	4558	65.5 ± 8.7[†]	50	78.3 ± 24.9[†]	24	-
Halper-Stromberg (2018) ECLIPSE [71]	1741	61.9 ± 7.9[†]	64	55.0 ± 26.1[†]	59	-
Landis (2018) CPRD [72]	27,557	71.1 ± 10.6	51.5	-	68.0[‡2]	Asthma history: 35.7
Llanos (2018) NHANES [73]	479	61 ± 0.4	56	84.2 ± 1.7[PreBD]	-	T1/2D: 15.9; CVD: 13.9
Ortega (2018) [107]	*11,329*	*70.1 ± 11.60*	*42.49*	*-*	*-*	*Asthma: 22.73; T1/2D: 30.18; CVD: 76.05; AR: 11.73*
Shin (2018) KOLD [74]	*299*	*66.8 ± 7.36*	*97.32*	*48.07 ± 15.30*	*40.47[‡1]*	*Asthma history: 28.09*
Turato (2018) [75]	*294*	*61.8 ± 8.21*	*-*	*68.0 ± 19.76[PostBD]*	*58.84[‡1]*	*-*
Zeiger (2018) [76]	7245	71.5 ± 9.6	57.1	-	ICS: 20.0	T1/2D: 22.8; CHF: 20.5; CAD: 22.7; Anxiety: 14.2; Depression: 22.1; Malignancy: 2.8
Acartürk Tunçay (2017) [77]	1066	67 (60–75)	60	31 (23–43) [n=345]	-	-
Casanova (2017) CHAIN/BODE [78]	*732*	*66.3 ± 8.94*	*82.51*	*59.85 ± 20.21*	*61.34[‡1]*	*-*
Hastie (2017) SPIROMICS [79]	*2499*	*-*	*54.46*	*68.42 (mean)[PreBD]*	*34.97[‡1]*	*Asthma history: 20.5*
Inoue (2017) [82]	1008	73.5 ± 8.3	93.0	56.7 ± 21.1	7.4 (+LABA: 40.1)	-
Kerkhof (2017) [80]	8318	70 ± 10	56.4	-	49.1	-
Kim (2017) KOLD [81]	307	75 (69–79)	97.1	52.9 ± 16.1[PostBD]	-	-
Oshagbemi (2017) [108]	39,824	69.4 ± 10.6	54.1	-	28.2	CVD: 23.6; OSP: 6.6; Anxiety: 15.1; Malignancy: 15.6
Song (2017) KOCOSS [83]	467	69.5 ± 7.4	95.9	55.5 ± 18.0	+LABA: 53.6	-
DiSantostefano (2016) NHANES (2007-2010) [84]	948	‖	59.7	-	-	Asthma history: 18.5; Asthma: 11.7
Kobayashi (2016) [85]	220	75.0 ± 7.0	92.3	61.4 ± 22.1	36.8	AR: 2.3
Suzuki (2016) Hokkaido COPD [86]	268	69 ± 8	94	65 ± 22[PostBD]	-	CVD: 22; IHD: 7; T1/2D: 5
Vedel-Krogh (2016) CGPS [87]	7225	64 (54–72)	50	78 (64–90)	7	T1/2D: 2; CVD: 9; Allergy: 20
Zeiger (2016) [109]	901	54.1 ± 8.8	37.4	-	89	Asthma: 79.5; AR: 35.8; NP±CRS: 4.2; Atopy: 1.3

*Entries in italic indicate publications for which data for the total population were calculated from the available published sub-group data (no data for the total population were originally reported)

[†]Mean ± SE

‖220 (32.3%) were under the age group 50–59 years

[‡]Data represent baseline values, unless otherwise indicated: [‡1]Time of assessment not reported; [‡2]Follow-up at 12 months

[§]CVD excludes high blood pressure; atopy includes eczema; perennial AR includes perennial allergen sensitization

Abbreviations: AR, allergic rhinitis; BD, bronchodilator; BODE, Body mass index, degree of airflow Obstruction, functional Dyspnoea and Exercise capacity; CAD, coronary artery disease; CGPS, Copenhagen General Population Study; CHAIN, COPD History Assessment In SpaiN; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; COSYCONET, COPD and SYstemic consequences-COmorbidities NETwork; CPRD, Clinical Practice Research Datalink; CRS, chronic rhinosinusitis; CVD, cardiovascular disease; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points; FEV$_1$, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; IHD, ischaemic heart disease; IQR, interquartile range (25th–75th percentile); KOCOSS, Korean COPD Subtype Study; KOLD, Korean Obstructive Lung Disease; LABA, long-acting β2-agonist; NHANES, National Health and Nutrition Examination Surveys; NP, nasal polyps; OSP, osteoporosis; SD, standard deviation; SE, standard error; SPIROMICS, Subpopulations and Intermediate Outcome Measures in COPD Study; T1/2D, type 1/2 diabetes

TABLE 1d Patient/subject characteristics for total populations (control and general population) from included articles

Author (year), study or cohort name* [reference]	N	Age, years, mean ± SD or median (IQR)	Male, %	FEV_1 % predicted, mean ± SD or median (IQR)	ICS use, %[‡]	Co-morbidities, %[§]
CONTROLS (n=7 articles and n=7 populations)						
Landis (2018) CPRD** [72]	27,557	71.1 ± 10.6	51.5	-	9.3[‡1]	Asthma history: 10.2
Burte (2017) EGEA2[‡‡] [45]	362	46.8 ± 16.3	50	107 (mean)	-	AR/hay fever: 5.5/10.8; Eczema: 22.7
Oshagbemi (2017)** [108]	90,772	69.9 ± 10.6	51.1	-	1.4	CVD: 28.5; OSP: 5.2; Anxiety: 12.2; Malignancy: 15.9
Racine (2017) [‡‡‖‖] [33]	237	50.2 ± 10.9	58.2	100.6 ± 14.4	27.4	Asthma history: 7.6; Atopy: 65.0
Vedel-Krogh (2017) CGPS[‡‡] [46]	76,440	58 (48–67)	45	97 (87–106)	2	Allergy: 25
DiSantostefano (2016) NHANES (2007-2010)** [84]	3123	‖	47.5	-	-	Asthma history: 4.5
Bouzigon (2012) EGEA[‡‡] [48]	783	46.6 ± 15.8	46.1	106.7 ± 16.5	0/3.5[Last 3/12 months]	AR: 22.1
GENERAL POPULATION (n=14 articles and n=14 populations)						
Bakrim (2018) [110]	*14,965*	*30.4 ± 9.72*	*52.99*	*-*	*-*	*-*
Dauchet (2018) ELISABET (2011-2013) [111]	1506	53.5 ± 7.2	44.8	-	-	-
Nerpin (2018) NHANES [112]	7753	47.5 (median)	51	97.0 ± 15.6	-	Asthma: 6.5
Omuse (2018) [113]	528	39.0 (20.0–63.0 [2.5th–97.5th %ile])	48.2	-	-	-
Wongkrajang (2018) [114]	*240*	*-*	*50.00*	*-*	*-*	*-*
Ozarda (2017) [115]	3363	‖1	47.9	-	-	-
Giovannelli (2016) ELISABET [116]	1579	53.3 ± 7.3	48.5	1.04 ± 0.18	1.1	Asthma: 7.3; Atopy: 32
Izuhara (2016) Nagahama [117]	9804	53.5 ± 13.4	33	-	-	Asthma: 4; COPD: 1; AR: 35
Vedel-Krogh (2016) CGPS [87]	81,668	58 (48–67)	45	96 (86–106)	5	T1/2D: 2; CVD: 6; Allergy: 28
Troussard (2014)[118]	*32,919*	*-*	*58.91*	*-*	*-*	*-*
Ko (2013) [119]	1093	47.3 ± 16.6	47.2	106.79 ± 13.87[PostBD]	-	Atopy positive: 59
Malinovschi (2013) NHANES [28]	12,408	36 (6–80)	51	-	4.0[‖2]	Asthma: 8.3; Hay fever: 13.7
Musk (2011) [120]	1969	54 ± 17	49.4	96.3 (mean)	-	Asthma: 18
Karita (2009) [121]	2105	28 (18–59)	51	-	-	-

Data are reported as mean ± SD, median (IQR), n or %, unless otherwise indicated. A dash (-) is used to indicate data that were not reported in the respective study/article

*Entries in italic indicate publications for which data for the total population were calculated from the available published sub-group data (no data for the total population were originally reported)

**Control population reported in the respective published study of COPD

[‡‡]Control population reported in the respective published study of asthma

[‖‖]Data for the respective asthma population were only available for subgroups that couldn't be combined, reported in Supplementary Results B

[§]CVD excludes high blood pressure; atopy includes eczema; perennial AR includes perennial allergen sensitization

[‡]Data represent baseline values, unless otherwise indicated; [‡1]Follow-up at 12 months

[‖]1,090 (40.9%) were under the age group 40–49 years; [‖1]2,914 (86.6%) between 20–59 years; [‖2]Use of ICS or OCS in the last two days

Abbreviations: %ile, percentile; AR, allergic rhinitis; BD, bronchodilator; CGPS, Copenhagen General Population Study; COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; CVD, cardiovascular disease; EGEA, Epidemiological study on the Genetics and Environment of Asthma; ELISABET, Investigation of Air and Breath in a Coastal Biological Environment; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; IQR, interquartile range (25th–75th percentile); Nagahama, Nagahama Prospective Genome Cohort for Comprehensive Human Bioscience; NHANES, National Health and Nutrition Examination Surveys; OCS, oral corticosteroid; OSP, osteoporosis; SD, standard deviation; T1/2D, type 1/2 diabetes

Supplementary Material

Supplementary Methods: Data handling

The following assumptions were made when deriving the number (n) and % with a measurement of the attribute, when not reported:

1. When n alone was recorded a percentage was derived from n and the number in the arm of the study.

2. When percentage alone was recorded, it was assumed that measurement was taken on all participants and the number with the attribute was derived from the percentage value and the number in the arm of the study.

3. When n was not provided and could not be derived, combined estimates of the mean and standard deviation (SD) for attributes were based on assuming all patients had a measurement taken.

4. Where a mean and confidence interval (CI) was provided, a SD was determined assuming all patients had a measurement taken.

Supplementary Results A: Description of articles for which total-population data were available

Characteristics and details of the eligible articles, including details of inclusion criteria, for which total population data were available (or could be calculated based on available data) are reported in Supplementary Table 2.

COPD (or other non-asthmatic chronic pulmonary disorders) or a history of heavy smoking were listed as exclusion criteria for 22 studies in asthma (16 studies excluded participants with COPD or other non-asthmatic chronic pulmonary disorders [1–16]; 6 studies excluded current smokers, individuals with a history of smoking >10 pack-years or with missing information on smoking history [17–22]) and 5 studies in severe asthma (4 studies excluded participants with COPD or other non-asthmatic chronic pulmonary disorders [2,18,23,24] and 1 study excluded participants with a smoking history >30 pack-years [25]).

Asthma

Of the 44 articles identified that included an asthma population, five reported data for sub-groups only and that could not be combined to create a total population because EOS data were reported only as medians (these are described below). Thus, of the 39 asthma studies that had total population data available/calculable, most were conducted in Europe (n=21), the USA (n=9) or South East Asia (n=7), with one study in New Zealand and one in Brazil; study sizes ranged from 200–363,558 participants, there were 15 studies with populations >1000 individuals, 14 of which were

conducted in the USA/Europe and one was conducted in Korea. Asthma was defined by spirometry in 11 studies [3,14,16,18,20,21,26,27,28–30], by physician report in 5 studies [7,11,17,31–32], was based on diagnostic codes from electronic medical records (EMR) in 7 studies [1,6,8–10,13,15], 7 studies specified international guidelines and/or current treatment to define severity [2,4,19,33–36] and the remaining 9 studies relied on patient self-reporting [5,22,37–43]. Fifteen studies included paediatric patients [1,8–11,13,15,16,18;29,30,36,37,40,44] while 17 studies were restricted to adults.

Severe Asthma
Two of the 14 articles with a severe asthma population only reported sub-group level data as median EOS and therefore could not be combined; thus 12 articles had total population data available. These studies were conducted in Europe (n=7), North America (n=4), and Brazil (n=1); study sizes ranged from 212–1,042 individuals and the single study with a population >1000 individuals was conducted in the UK. Severe asthma was defined by spirometry in 3 studies [18,45,71], was based on EMR diagnostic codes in another 2 studies [23,46]; the remaining 8 studies used international guidelines and/or current treatment to define severity. Four studies included paediatric patients [18,23,25,45], while 7 studies were restricted to adults only.

COPD
All 23 COPD studies had total population data available/calculable, were conducted in the USA (n=8), Europe (n=10), and Asia (n=7) (two studies reported data from cohorts in both the USA and Europe). Study sizes ranged from 220–39,824 participants and there were 11 studies with populations >1000 individuals, nine of which were conducted in the USA/Europe and two were conducted in Asia (Japan and Turkey). COPD was defined by spirometry in 20 studies [21,37,47–64], and was based on EMR diagnostic codes in 3 studies [12,65,66]. One study included patients aged ≤35 years.

Control and General Populations
Control populations were reported in 10 of the studies that investigated asthma, severe asthma, and/or COPD populations; two of these 10 only reported sub-group level data as median EOS and thus could not be combined. Total population data were therefore available for eight control populations, which were based in Europe (n=6) and North America (n=2), and ranged in size from 178–90,772 individuals. All 8 studies were restricted to adults.

Of the 16 studies reporting a general population, two of which only reported sub-group level data as median EOS and thus could not be combined, 14 reported total population data and had widespread

sources including African countries (n=3), Europe (n=4), the USA (n=2), Asia (n=4) and Australia (n=1), ranging in size from 240–81,668 participants. There were 12 studies with populations >1000 individuals, six of which were conducted in the USA/Europe, three were conducted in Asia (Hong Kong, Japan, and Turkey), two were conducted in Africa (Morocco, and multiple African countries, and one was conducted in Australia. One study included paediatric patients (aged 6–80 years [44] while 12 studies were restricted to adults.

Supplementary Results B: articles for which only median sub-group blood EOS counts were available

Asthma
Five asthma studies reported data as median (IQR) EOS that could not be combined (non-occupational asthma, 200 cells/µL [200] and occupational asthma, 200 cells/µL [300] [67]; adults with no asthma exacerbations, 201 cells/µL [121–315], adults with 1–2 asthma exacerbations, 207 cells/µL [130–372] and adults with ≥3 asthma exacerbations, 230 cells/µL [116–442] [68]; never-smoker with airflow limitation with asthma, 270 cells/µL [170–400] and never-smoker without airflow limitation with asthma, 210 cells/µL [130–330] [69]; eosinophilic asthma, 315 cells/µL [202–513], neutrophilic asthma, 129 cells/µL [79–228], mixed granulocytic asthma, 289 cells/µL [216–449] and paucigranulocytic asthma, 140 cells/µL [85–227] [70]; paucigranulocytic asthma, 160 cells/µL [0–1220], eosinophilic asthma, 360 cells/µL [0–3220], neutrophilic asthma, 170 cells/µL [20–1020] and mixed granulocytic asthma, 420 cells/µL [190–3040] [71]).

Severe Asthma
Two severe asthma studies reported data as median (IQR) EOS that could not be combined (non-smokers with severe asthma, 0.2 [0.3] [no units] [N=302] and current/ex-smokers with severe asthma, 0.22 [0.29] [no units] [N=106] [72]; never smokers with severe asthma, 270 cells/µL [100–550], exsmokers with severe asthma, 300 cells/µL [120–580] and current smokers with severe asthma 210 cells/µL [120–400] [73]).

Control and General Populations
Two studies with control populations reported data as median (IQR) EOS that could not be combined (healthy never smokers, 150 cells/µL [100–220] and healthy ever smokers, 160 cells/µL [110–240] [21]; non-asthmatic never-smokers with airflow limitation, 170 cells/µL [110–250] and non-asthmatic never-smokers without airflow limitation, 160 cells/µL [110–240] [69]).

Two general population studies reported data as median EOS that could not be combined (male healthy adult volunteers, 100 cells/µL [95th percentile: 0.0–1000] female healthy adult volunteers, 130 cells/µL [95th percentile: 10–1090] [74]; males aged <60 years 0.029 [units given as 'fraction'] [IQR: 0.018–0.046], males aged ≥60 years 0.028 [units given as 'fraction'] [IQR: 0.017–0.045] females aged <60 years 0.021 [units given as 'fraction'] [IQR: 0.014–0.034], females aged ≥60 years 0.022 [units given as 'fraction'] [IQR: 0.015–0.034] [75]).

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Supplementary Table 1. Search strategy for PubMed to identify articles reporting blood EOS data for (a) disease populations, and (b) general populations

a. Disease (asthma and COPD) populations

Description	Search string	Results
COPD	(pulmonary disease, chronic obstructive[MeSH Terms]) OR ("chronic airflow obstruction"[Title/Abstract] OR emphysema[Title/Abstract] OR "chronic bronchitis"[Title/Abstract] OR "chronic obstructive pulmonary disease"[Title/Abstract] OR coad[Title/Abstract] OR copd[Title/Abstract] OR "chronic obstructive airway disease"[Title/Abstract])	92,728
Asthma	(asthma[MeSH Terms]) OR asthma[Title/Abstract]	163,679
Total disease (COPD and asthma) population	(((asthma[MeSH Terms]) OR asthma[Title/Abstract])) OR ((pulmonary disease, chronic obstructive[MeSH Terms]) OR ("chronic airflow obstruction"[Title/Abstract] OR emphysema[Title/Abstract] OR "chronic bronchitis"[Title/Abstract] OR "chronic obstructive pulmonary disease"[Title/Abstract] OR coad[Title/Abstract] OR copd[Title/Abstract] OR "chronic obstructive airway disease"[Title/Abstract]))	242,856
Eosinophil associated keywords	(((Eosinophils[MeSH Terms]) OR eosinop*)) AND blood	41,517
Total disease population AND Eosinophil associated keywords	(((((asthma[MeSH Terms]) OR asthma[Title/Abstract])) OR ((pulmonary disease, chronic obstructive[MeSH Terms]) OR ("chronic airflow obstruction"[Title/Abstract] OR emphysema[Title/Abstract] OR "chronic bronchitis"[Title/Abstract] OR "chronic obstructive pulmonary disease"[Title/Abstract] OR coad[Title/Abstract] OR copd[Title/Abstract] OR "chronic obstructive airway disease"[Title/Abstract]))) AND ((((Eosinophils[MeSH Terms]) OR eosinop*)) AND blood)	10,605
Time and Language filter	(((((asthma[MeSH Terms]) OR asthma[Title/Abstract])) OR ((pulmonary disease, chronic obstructive[MeSH Terms]) OR ("chronic airflow obstruction"[Title/Abstract] OR emphysema[Title/Abstract] OR "chronic bronchitis"[Title/Abstract] OR "chronic obstructive pulmonary disease"[Title/Abstract] OR coad[Title/Abstract] OR copd[Title/Abstract] OR "chronic obstructive airway disease"[Title/Abstract]))) AND ((((Eosinophils[MeSH Terms]) OR eosinop*)) AND blood) Filters: Publication date from 2008/01/01; English	4,323

b. General populations

Description	Search string	Results
Population	("general population") OR healthy volunteers[MeSH Terms]	102,108
Eosinophil associated keywords	(((Eosinophils[MeSH Terms]) OR eosinop*)) AND blood	41,517
Population AND Eosinophil associated	((("general population") OR healthy volunteers[MeSH Terms])) AND ((((Eosinophils[MeSH Terms]) OR eosinop*)) AND blood)	103

keywords		
Time and Language filter	((("general population") OR healthy volunteers[MeSH Terms])) AND ((((Eosinophils[MeSH Terms]) OR eosinop*)) AND blood) Filters: Publication date from 2008/01/01; English	62

Supplementary Table 2. Study details for included articles for which data for total populations were available, by population type

Author (year) [reference], Study or cohort name*	Country	Inclusion criteria†
ASTHMA (n=39 articles and n=40 populations)		
Amaral (2018) [1] NHANES	USA	Adults with current asthma, defined as a positive answer to: "Has a doctor ever told you that you have asthma?" and "Do you still have asthma?", and either "wheezing/whistling in the chest in the past 12 months" or "asthma attack in the past 12 months."
Calciano (2018) [2] GEIRD	Italy	Asthma defined as ≥1 of the following: 1) physician-diagnosed asthma; and 2) asthma-like symptoms or anti-asthmatic treatment in the past 12 months, and having ≥1 of the following: a. PC20 ≤1 mg; b. pre-BD airflow obstruction (FEV$_1$/FVC <70% or <LLN,) and a positive reversibility test; c. pre- but not post-BD airflow obstruction, and post-BD FEV$_1$ ≥80%
Çolak (2018) [3] CGPS	Denmark	Aged 20–100 years; pre-BD FEV$_1$/FVC ≥0.70 and self-reported asthma, or pre-BD FEV$_1$/FVC <0.70 and post-BD FEV$_1$/FVC ≥0.70, or pre- and post-BD FEV$_1$/FVC <0.70 and FEV$_1$ reversibility of >12% and >400 mL and <10 pack-years of smoking history
Kerkhof (2018) [4] CPRD/OPCRD	UK	Aged ≥5 years at most recent asthma diagnosis; active asthma defined as a diagnostic Read code for asthma qualifying for inclusion in asthma registry; ≥1 blood EOS count after diagnosis and ≥2 years of continuous data
Kumar (2017) [5]	*India*	*Asthma diagnosed according to GINA criteria; enrolment from outpatient clinics*
Lima-Matos (2018) [6]	Brazil	Aged ≥18 years; mild to moderate asthma, most controlled without current ICS and a few using low-dose ICS with no other controller
Llanos (2018) [7] NHANES	USA	Aged ≥12 years; ≥1 blood EOS count; asthma defined as ever being told by a physician they had/have asthma, or had an episode of asthma or asthma attack in past 12 months
Mäkelä (2018) [8]	Finland	Adults with physician diagnosed asthma; data available in the Auria Biobank Research Database; ≥1 blood EOS count
Papi (2018) [9]	UK	Aged ≥18 years with moderate to severe asthma with ≥1 year of continuous data and prior diagnosis of asthma; GINA step 3 or 4; ≥2 ICS prescriptions during baseline year; blood EOS
Semprini (2018) [10]	New Zealand	Adults with asthma from the New Zealand Respiratory Health Survey phase two and longitudinal study of serum periostin levels
Seo (2018) [11]	*Korea*	*Asthma diagnosed using the GINA 2008; one or more of: >20% variability in PEF over 14 days, >12% and >200 mL increase in FEV$_1$ after 200-400 µg albuterol, or 20% reduction in FEV$_1$ after <10 mg/mL methacholine*
Teague (2018) [12] SARP III	USA	Aged ≥6 years with physician diagnosis of asthma that was non-severe according to a modification of ERS/ATS consensus definition; treated with high-dose ICS for ≥6 of prior 12 months and the 3 months before enrolment); BD reversibility ≥12%, or airway hyperresponsiveness
Akiki (2017) [13] EGEA II	France	Self-reported positive responses to four questions from the standardized BMRC, European Coal and Steel Community, ATS and ECRHS questionnaires; data for serum cytokines
Blakey (2017) [14]	UK	Aged 12–80 years; active asthma defined as ≥2 prescriptions for asthma drugs during study year 1, and no Read code for resolved asthma during 3-year study; ≥3 years of continuous data
Burte (2017) [15] EGEA	*France*	*Asthma status based on a positive answer to either 'Have you ever had attacks of breathlessness at rest with wheezing?' or 'Have you ever had asthma attacks?', or as originally being recruited to EGEA as an asthma case; data on asthma, rhinitis, skin-prick test, total IgE, and blood EOS*
Casciano (2017) [16]	*USA*	*Aged ≥12 years with asthma diagnosis*
Kimura (2017) [17]	Japan	Asthma subjects for at least one year by a respiratory physician
Pretolani (2017) [18] COBRA	France	Mild-moderate-severe asthma, aged 18–85 years
Vedel-Krogh (2017) [19] CGPS	Denmark	A positive answer to the question: "Do you have asthma?"
Zeiger (2017) [20]	USA	Aged 18–64 years; persistent asthma required one of the following: asthma hospitalization, asthma ED visit, ≥4 asthma outpatient visits and ≥2 asthma drugs dispensed, or ≥4 asthma drugs dispensed; continuous health plan enrolment and pharmacy benefit
Casciano (2016) [21]	*USA*	*Aged ≥12 years with asthma diagnosed as ICD-9-CM code 493.xx, who had ≥2 encounters in the ED, outpatient or inpatient setting*

de Groot (2016) [22]	Netherlands	Aged ≥18 years; diagnosis confirmed by reversible airway obstruction or by airway hyperresponsiveness; treatment with medium–high-dose ICS; no asthma exacerbations or RTI in prior 4 weeks; smokers and ex-smokers could participate if they had asthma symptoms, and a normal diffusion capacity of CO (≥80% predicted)
Nadif (2016) [23]	*France*	*Aged ≥16 years with data for blood EOS and neutrophils; positive responses to four questions from the standardised BMRC, European Coal and Steel Community, ATS and ECRHS questionnaires*
Pola-Bibian (2016) [24]	Spain	Aged >14 years who attended the ED with an ICD-9-CM code for asthma
Price (2016) [25]	UK	Aged 12–80 years treated in UK clinical practice; ≥1 valid blood EOS count, 1 full year of data on each side of the index blood EOS count
Price (2015) [26]	USA	Aged 12–80 years with an asthma diagnostic Read code, a recorded blood EOS count, and 1 year of continuous records both before and after their most recent blood EOS count
Tuomisto (2016) [27] SAAS	Finland	New-onset asthma diagnosed at adult age, made by a respiratory specialist confirmed by ≥1 objective lung function measurements; had symptoms of asthma; aged ≥15 years
Westerhof (2015) [28]	Netherlands	Confirmed adult-onset asthma based on international guidelines; included in three clinical trials
Agarwal (2014) [29]	India	Aged ≥15 years with bronchial asthma; two of the following: history of recurrent attacks of cough or SoB or chest tightness, wheeze on chest auscultation, and spirometric obstruction (FEV_1/FVC < LLN) with the presence of BD reversibility
Lee (2014) [30]	*Korea*	*Asthma defined by the ATS criteria; current symptoms, including wheezing, dyspnoea, and cough; airway reversibility and/or airway hyperresponsiveness*
Schleich (2014) [31] Retrospective/prospective	Belgium	Retrospective cohort: aged ≥18 years with asthma diagnosed based on presence of cough, SoB or dyspnoea, plus demonstration of airflow variability; successful sputum induction; Prospective cohort: newly recruited asthma patients matched to the retrospective cohort
Tran (2014) [32] NHANES	USA	Providing an affirmative response to these questions: "Has a physician or other health professional ever told you that you have asthma?" and "Do you still have asthma?"; complete blood cell count data, including absolute counts of EOS and neutrophils
Ali (2013) [33]	*Denmark*	*Adults; history consistent with asthma, with attacks of SoB and/or wheezing, chest tightness and dry cough either spontaneously or triggered by exercise, allergens, RTI, or irritants; reversibility in FEV_1 >15% (and ≥150 mL); diurnal variability in PEF rate >20% (and ≥100 L/min)*
Amelink (2013) [34]	Netherlands	Aged 20‒75 years with adult-onset asthma defined according to GINA criteria; stable on asthma medication (no exacerbations or changes in asthma medication in past 4 weeks)
Hastie (2013) [35] SARP	*USA*	*Mild or moderate asthma*
Park (2013) [36] COREA	*Korea*	*Asthmatics diagnosed according to GINA criteria; elderly asthma defined as being aged ≥65 years, non-elderly asthma defined as being aged ≥14‒<65 years [37]*
Bouzigon (2012) [38] EGEA	France	'Current asthma' defined as respiratory symptoms in the past 12 months (wheeze, nocturnal chest tightness, SoB following strenuous activity, at rest or at night, and asthma attacks) or use of inhaled and/or oral medicines due to breathing problems
Matsunaga (2012) [39]	Japan	Aged ≥20 years; stable asthma with ICS with/without inhaled LABA, LTRA, or theophylline; poorly controlled asthma, one of: ACT <20, FEV_1 <80% predicted, or PEF <80% variability
Nadif (2009) [40] French EGEA	France	Defined as a positive answer to four standardised questions: ''Have you ever had attacks of breathlessness at rest with wheezing?'', ''Have you ever had asthma attacks?'', ''Was this diagnosis confirmed by a doctor?'', ''Have you had an asthma attack in the last 12 months?''
SEVERE ASTHMA (n=12 articles and n=12 populations)		
Haughney (2018) [41]	UK	Aged ≥18 years with severe asthma defined as an ever-recorded Read code/ICD code for asthma, plus ≥1 prescription for any of: SABA, ICS, ICS/LABA; ≥1 serum IgE
Heffler (2019) [42] SANI	Italy	Aged >12 years with severe asthma diagnosed according to the ERS/ATS criteria; clinically uncontrolled (altered ACT and/or ACQ), or experiencing ≥2 acute asthma exacerbations per year (or ≥1 severe exacerbation requiring ED admission, or hospitalization or intubation), or FEV_1 <80% predicted, despite high dose ICS plus another controller or OCS for ≥6 months in the prior year
Husereau (2018) [43]	Canada	Aged ≥12 years with severe asthma as per prescriptions for high-dosage ICS plus either a LTRA, LABA, or theophylline filled on the same day; ≥2 asthma diagnoses identified by OHIP diagnosis code 493
Lima-Matos (2018) [6]	Brazil	Aged ≥18 years with untreated severe asthma according to a classification proposed to WHO; two additional inclusion criteria: ≥6 months of follow-up in ProAR reference clinic and not possible to taper down ICS dose to < medium dose of BUD or equivalent in combination with LABA during the follow-up
Maio (2018) [44] RItA	Italy	Severe/uncontrolled asthma according to the WHO Consultation on Severe Asthma
Teague (2018) [12] SARP III	USA	Aged ≥6 years; severe asthma defined according to a modification of ERS/ATS consensus definition, with those treated with high-dose ICS for ≥6 of prior 12 months and the 3 months before enrolment were assigned as severe; BD reversibility ≥12%, or airway hyperresponsiveness

Chipps (2018) [45] TENOR II	USA	Aged ≥6 years with severe or difficult-to-treat asthma from TENOR I study; treated for ≥1 year with either high health care use (>2 unscheduled asthma care visits or >2 OCS bursts) or high medication use (requiring >3 asthma controller medications, long-term daily high ICS, or use of >5 mg/d oral prednisone) in prior 12 months
Pretolani (2017) [18] COBRA	*France*	*Aged 18–85 years with severe asthma (GINA steps 4 and 5)*
Zeiger (2017) [46]	USA	Aged ≥12 years with persistent asthma (defined by HEDIS criteria) and met criteria for severe untreated asthma (2 asthma exacerbations, 6 medium or high-dose ICS canisters as monotherapy or in combination with LABA, and 3 non-ICS controller canisters); continuous health plan enrolment and pharmacy benefit (no enrolment gap of >45 days within a calendar year)
Chaudhuri (2016) [47]	UK	Aged ≥18 years with severe refractory asthma, defined based on the ERS/ATS guidelines, from the BTS Severe Asthma Registry
Newby (2014) [48] BTS Severe refractory Asthma	UK	Centres contributing to BTS Severe Asthma Registry; Severe refractory asthma defined by OCS >50% of the time or high-dose ICS (plus add on medications)
Schleich (2014) [49] BSAR	Belgium	Age ≥18 years with severe asthma defined according to ATS criteria (requires one major criterion, either treatment with continuous or near continuous OCS or a combination of high dose ICS and LABA; asthma follow-up for ≥12 months

COPD (n=23 articles and n=24 populations)

Chalmers (2018) [50]	*UK*	*Aged ≥40 years; new diagnosis of COPD (any Read code for COPD, confirmed by spirometry [FEV$_1$/FVC <0.7]) and classified as GOLD A/B; prescription of maintenance BD ≤3 months of diagnosis; ≥1 full year of data*
Çolak (2018) [3] CGPS	Denmark	Aged 20–100 years; COPD: pre- and post-BD FEV$_1$/FVC <0.70 and no self-reported asthma or FEV$_1$ reversibility
Greulich (2018) [51] COSYCONET	Germany	COPD and a differential blood cell count; assessments at each clinic visit in the COSYCONET study include clinical history, spirometry and blood samples [52]
Halper-Stromberg (2018) [53] COPDGene/ECLIPSE	USA; UK	COPDGene: aged 45–80 years with COPD as per GOLD classification and ≥10-pack-year smoking history; ECLIPSE: aged 40–75 years with COPD (FEV$_1$ <80% and FEV$_1$/FVC ≤0.7) and ≥10-pack-year smoking history
Landis (2018) [54] CPRD	UK	Aged ≥40 years with spirometry confirmed (FEV$_1$/FVC <0.7) diagnosis for COPD; ≥12 months history before the index date; ≥1 blood EOS count during the stable disease state within 6 months of the index date
Llanos (2018) [7] NHANES	USA	≥12 years with COPD (spirometry as per GOLD 2016, FEV$_1$/FVC <0.70 after inhaling BD medication, had chronic bronchitis or had emphysema); ≥1 blood EOS count available
Ortega (2018) [55]	*USA*	*Aged ≥40 years; ≥1 COPD-related code in prior year; ≥1 prescription for inhaled maintenance therapy and continuous clinical activity during year of interest*
Shin (2018) [56] KOLD	*Korea*	*Aged ≥40 years with COPD, defined as post-BD FEV$_1$/FVC <0.7 and smoking history of >10 pack-years; baseline and serial EOS counts*
Turato (2018) [57]	*Spain*	*Smokers >40 years with COPD followed for ≥ 5 years*
Zeiger (2018) [58]	USA	Aged ≥40 years with HEDIS-defined COPD , with post-BD FEV$_1$/FVC <0.7; blood EOS count; continuous KPSC health plan enrolment and pharmacy coverage for the 1-year baseline period before index date
Acartürk Tunçay (2017) [59]	Turkey	COPD diagnosed by a pulmonologist; airflow obstruction on spirometry (FEV$_1$ ≤70% predicted, FEV$_1$/FVC ≤70%) and a compatible history for COPD; admitted to ICU outpatient clinic due to CRF); complete blood count
Casanova (2017) [60] CHAIN and BODE cohorts	*USA; Spain*	*COPD defined by a smoking history ≥10 pack-years and post-BD FEV$_1$/FVC <0.7; CHAIN: stable for ≥6 weeks and receiving optimal medical therapy; BODE: clinically stable and receiving therapy according to international guidelines*
Hastie (2017) [61] SPIROMICS	*USA*	*Aged 40–80 years; COPD defined as a post-BD FEV$_1$/FVC <0.7; current or former history of tobacco use (>20 pack-year) and non-smokers*
Inoue (2017) [62]	Japan	Aged ≥40 years; stable COPD diagnosed according to GOLD criteria; FEV$_1$/FVC <0.7; current or ex-smoker, history of ≥10 pack-years; ≥1 year medical records with spirometry; airway reversibility or spirometry data on 2 occasions in past 3 years
Kerkhof (2017) [63]	UK	Aged ≥40 years; COPD defined as FEV$_1$/FVC <0.70 recorded within 5 years of index date; ≥1 blood EOS count measured at stable disease (no COPD exacerbation in prior/subsequent 4 weeks); history of cigarette smoking and ≥1 year of data before and after index date
Kim (2017) [64] KOLD	Korea	Aged >40 years with stable COPD diagnosed according to ATS and GOLD criteria; smoked >10 pack-years; post-BD FEV$_1$/FVC <0.7; no abnormalities on chest radiograph
Song (2017) [65] KOCOSS	Korea	Aged >40 years; COPD defined as post-BD FEV$_1$/FVC <0.7; smoked >10 years; non-ACOS COPD after excluding ACOS patients according to Spanish criteria
Oshagbemi (2017) [66]	UK	Aged ≥40 years; COPD recorded by a read code; ≥2 blood EOS counts on different dates
Kobayashi (2016) [67]	Japan	Aged 40–90 years with stable COPD diagnosed according to GOLD criteria; no asthma symptoms; former smokers with a history of ≥10 pack-years
DiSantostefano (2016) [68] NHANES (2007-2010)	USA	Aged ≥40 years with COPD; categorised by GOLD 2006 as FEV$_1$/FVC <0.7 and FEV$_1$ ≥80%; non-missing EOS counts; EOS % as a function of total white blood cells

Suzuki (2016) [69] Hokkaido COPD Study	Japan	Aged ≥40 years with respiratory specialist-diagnosed COPD; data on BD reversibility, blood EOS count, and specific IgE; current/former smokers with smoking history of ≥10 pack-years
Vedel-Krogh (2016) [70] CGPS	Denmark	FEV_1/FVC <LLN; FEV_1/FVC <70%; no self-reported asthma
Zeiger (2016) [71] HEDIS	USA	HEDIS-defined 2-year asthma-COPD; continuous health plan enrolment and pharmacy benefit
CONTROLS [non-asthma, non-COPD] (n=7 articles and n=7 populations)		
Landis (2018) [54] CPRD‡	UK	Matched 1:1 on sex, smoking, and age (to COPD patients); no code for COPD diagnosis recorded; 12-month history in the CPRD and 1 blood EOS count ≤6 months of index date
Burte (2017) [15] EGEA2§	France	Data on SPT, total IgE, and blood EOS; subjects without asthma or rhinitis
Oshagbemi (2017) [66]‡	UK	Matched to COPD patients by sex, year of birth, and medical practice; ≥2 blood EOS counts on different dates
Racine (2017) [72]§‖	Canada	No airflow limitation and PC20 >16 mg/mL
Vedel-Krogh (2017) [19] CGPS§	Denmark	Aged 20–100 years were randomly selected from the general population for the CGPS
DiSantostefano (2016) [68] NHANES (2007-2010)‡	USA	Aged 40–79 years with 'normal' lung function, defined as no restriction, and no self-reported current asthma, chronic bronchitis, emphysema, and/or bringing up phlegm on most days in the prior 3 months; recorded EOS counts
Bouzigon (2012) [38] EGEA§	France	Population-based controls
GENERAL POPULATION (n=14 articles and n=14 populations)		
Bakrim (2018) [73]	*Morocco*	*Women aged 18–50 years and men aged 18–55 years from the Tangier-Tetouan region*
Dauchet (2018) [74] ELISABET (2011-2013)	France	Aged 40–65 years; residence in the same city or its surrounding urban area (either Lille or Dunkirk) for ≥5 years
Nerpin (2018) [75] NHANES 2007–2010	USA	Aged 20–80 years who underwent spirometry testing, laboratory studies and responded to questions about respiratory symptoms and smoking habits
Omuse (2018) [76]	Kenya	Black African urban population aged 18–65 years who had undergone an overnight fast
Wongkrajang (2018) [77]	*Thailand*	*Male or non-pregnant and non-breastfeeding females aged 18–60 years*
Ozarda (2017) [78]	Turkey	Aged 18–79 years; health participants ideally not on any medications except contraceptive pills or oestrogens and thyroxine [79]
Giovannelli (2016) [80] ELISABET	France	Aged 40–64 years; resident in Dunkirk or the Dunkirk urban area for ≥5 years
Izuhara (2016) [81] Nagahama Study	Japan	Citizens in Nagahama City in Japan; no current serious diseases, were able to live independently
Vedel-Krogh (2016) [70] CGPS	Denmark	Aged 20–100 years; randomly selected from the general population on the basis of the national Danish Civil Registration System; full spirometry and blood EOS data
Troussard (2014) [82]	*France*	*Aged 16–69 years and had a periodic health assessment at the Inter-Regional Health Institute*
Ko (2013) [83]	Hong Kong, China	Aged 18–90 years; not current smokers; previous smokers must have stopped smoking for ≥1 year with a smoking history of <10 pack-years
Malinovschi (2013) [84] NHANES 2007–2010	USA	Aged 6–80 years with data on exhaled NO measurements and blood differential counts
Musk (2011) [85]	Australia	Adults from the electoral register of Busselton, Australia
Karita (2009) [86]	African countries	Aged 18–60 years; HIV-negative test

ABPA, allergic bronchopulmonary aspergillosis; ACOS, asthma-COPD overlap syndrome; ACT, asthma control test; ACQ, Asthma control questionnaire; ATS, American Thoracic Society; BD, bronchodilator; BMI, body mass index; BMRC, British Medical Research Council; BODE, body mass index, degree of airflow obstruction, functional dyspnoea and exercise capacity index; BSAR, Belgian Severe Asthma Registry; BTS, British Thoracic Society; BUD, budesonide; CGPS, Copenhagen General Population Study; C-RIDL; Committee on Reference Intervals and Decision Limits; CHAIN, COPD History Assessment In SpaiN; CO, carbon monoxide; COBRA, COhort of BRonchial obstruction and Asthma; COPD, chronic obstructive pulmonary disease; COREA, Cohort for Reality and Evolution of Adult Asthma in Korea; COSYCONET, COPD and SYstemic consequences-COmorbidities NETwork; CPRD, Clinical Practice Research Datalink; CRF, chronic respiratory failure; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points; ECRHS, European Community Respiratory Health Survey; ED, emergency department; EGEA, Epidemiological study on the Genetics and Environment of Asthma; ELISA, enzyme-linked immunosorbent assay; ELISABET, Enquête Littoral Souffle Air Biologie Environnement survey; EOS, eosinophil; ERS, European Respiratory Society; FeNO, fractional concentration of exhaled nitric oxide; FEV1, forced expiratory volume in one second; FP, fluticasone propionate; FVC, forced vital capacity; GEIRD, Gene Environment Interactions in Respiratory Diseases; GINA, Global Initiative for Asthma; HEDIS, Healthcare Effectiveness Data and Information Set; ICD-9, International Classification of Diseases version 9; ICD-10, International Classification of Diseases version 10; ICS, inhaled corticosteroid; ICU, intensive care unit; IFCC, International Federation of Clinical Chemistry; IgE, immunoglobulin E; KOCOSS, Korean COPD Subtype Study; KOLD, Korean Obstructive Lung Disease; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; LLN, lower limit of normal; LTOT, long-term oxygen therapy; LTRA, leukotriene receptor antagonist; MIDAS, Minimally-Invasive Diagnostic procedures in allergy, Asthma, or food hypersensitivity Study; Nagahama, Nagahama

Prospective Genome Cohort for Comprehensive Human Bioscience; NHANES, National Health and Nutrition Examination Surveys; NIMV, non-invasive mechanical ventilation; NO, nitric oxide; NZRHS, New Zealand Respiratory Health Survey; OCS, oral corticosteroid; OPCRD, Optimum Patient Care Research Database; PC20, provocation concentration producing a 20% fall in FEV_1; PEF, peak expiratory flow; PFT, pulmonary function test; PREDUNA, Predictors of Uncontrolled Asthma; RItA (acronym from the Italian words standing for Italian Registry of SUA); RTI, respiratory tract infection; SAAS, Seinäjoki Adult Asthma Study; SABA, short-acting β2-agonist; SANI, Severe Asthma Network in Italy; SARP, Severe Asthma Research Program; SIC, specific inhalation challenge; SoB, shortness of breath; SPIROMICS, Subpopulations and Intermediate Outcome Measures in COPD Study; TENOR, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens; UK, United Kingdom; USA, United States of America

*Entries in italics indicate publications for which data for the total population were calculated from the available published sub-group data

†Criteria listed are not exhaustive of all criteria described in each study/publication. Further details are available in the respective publications

‡Control population reported in the respective published study of COPD

§Control population reported in the respective published study of asthma

‖Data for the respective asthma population were only available for subgroups that couldn't be combined, reported in Supplementary Results B

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Supplementary Table 3. Blood EOS counts (means/medians) for total populations from included articles, by population type

Author (year) [reference], study or cohort name*	Country; Sample size	EOS count (cells/µL)†		Author (year) [reference], study or cohort name*	Country; Sample size	EOS count (cells/µL)†	
		Median (25th–75th %ile)	Arithmetic mean (± SD)			Median (25th–75th %ile)	Arithmetic mean (± SD)
ASTHMA (n=34 articles and n=35 populations)							
Calciano (2018) [1] GEIRD	Italy; N=287	165.2 (99.5–261.0)	-	*Nadif (2016) [19]*	*France; N=716*	-	*257.7 ± 194.9*
Çolak (2018) [2] CGPS	Denmark; N=449	160 (110–270)	-	Price (2016) [20]	UK ; N=130,547	200 (120–350)	-
Kerkhof (2018) [3] CPRD/OPCRD	UK; N=363,558	200 (110–350)	-	Tuomisto (2016) [21] SAAS	Finland; N=203	280 (150–420)	-
Kumar (2017) [4]	*India; N=463*	-	*507.9 ± 283.8*	Price (2015) [22]	USA; N=130,248	200 (120–340)	-
Lima-Matos (2018) [5]	Brazil; N=452	235 (131–399)	-	Westerhof (2015) [23]	Netherlands; N=336	200 (100–300)	-
Llanos (2018) [6] NHANES	USA; N=1,609	-	233 ± 7	Agarwal (2014) [24]	India; N=296	298 (174.5–500)	-
Mäkelä (2018) [7]	Finland, N=4,357	270 (50–1,040)[a]	-	*Lee (2014) [25]*	*Korea; N=533*	-	*417.3 ± 304.5*
Papi (2018) [8]	UK; N=7,195	200 (120–320)	-	Schleich (2014) [26] Retrospective	Belgium; N=508	230 (0–3,220)§	-
Semprini (2018) [9]	New Zealand; N=212	-	250 ± 190	Schleich (2014) [26] Prospective**	Belgium; N=250	188 (0–1,133)§	-
Seo (2018) [10]	*Korea; N=323*		*475.9 ± 40.9*	Tran (2014) [27] NHANES	USA; N=1,721	157 (75–267)	248 ± 6‡
Teague (2018) [11] SARP III	USA; N=213	189 (111–320)		*Ali (2013) [28]*	*Denmark; N=1,075*	-	*441.8 ± 354.1*
Akiki (2017) [12] EGEA II	France; N=283	-	215 (140, 320)‖	Amelink (2013) [29]	Netherlands; N=200	200 (100–340)	-
Burte (2017) [13] EGEA	*France; N=501*	-	*245.0 ± 186.7*	*Hastie (2013) [30] SARP*	*USA; N=257*	-	*254.4 ± 195.0*
Kimura (2017) [14]	Japan; N=206	-	215 (0.44)††	*Park (2013) [31] COREA*	*Korea; N=2,067*	-	*292.0 ± 322.7*
Pretolani (2017) [15] COBRA	France; N=1,080	230 (120–440)	-	Bouzigon (2012) [32] EGEA	France; N=494	200 (140–320)	-
Vedel-Krogh (2017) [16] CGPS	Denmark; N=4,838	220 (140–340)	-	Matsunaga (2012) [33]	Japan; N=229	-	251 ± 209
Zeiger (2017) [17]	USA; N=9,546	-	263 ± 280	Nadif (2009) [34] French EGEA	France; N=381	-	275 ± 200
de Groot (2016) [18]	Netherlands; N=491	200 (100–300)	-				
SEVERE ASTHMA (n=11 articles and n=11 populations)							
Haughney (2018) [35]	UK; N=884	400 (200–700)[c]	-	Chaudhuri (2016) [39]	UK; N=1,042	280 (110–540)	-
Heffler (2019) [36] SANI	Italy; N=437	-	536.7 ± 650.9	Chipps (2018) [40] TENOR II	USA; N=341	200 (200)‡‡	200 ± 144
Husereau (2018) [37]	Canada; N=212	-	303 ± 266[b]	Zeiger (2017) [41]	USA; N=261	-	364 ± 416
Lima-Matos (2018) [5]	Brazil; N=544	248 (141–384)	-	Newby (2014) [42] BTS Severe refractory Asthma	UK; N=349	300 (490)‡‡	-
Maio (2018) RItA [38]	Italy; N=493	300.0 (170.0–495.0)	-	Schleich (2014) [43] BSAR	Belgium; N=350	240 (0–3,144)§	-
Teague (2018) [11] SARP III	USA; N=313	228 (134–399)	-				
COPD (n=17 articles and n=18 populations)							
Çolak (2018) [2] CGPS	Denmark; N=404	180 (120–260)	-	Acartürk Tunçay (2017) [50]	Turkey; N=1,066	150 (90–230)	-
Halper-Stromberg (2018) [44] COPDGene	USA; N=4,558	-	200 ± 100‡	Inoue (2017) [51]	Japan; N=1,008	-	239.1 ± 234.6
Halper-Stromberg (2018) [44] ECLIPSE**	UK; N=1,741		200 ± 100‡	Kim (2017) [52] KOLD	Korea; N=307	183.5 (111.5–316.5)	-
Landis (2018) [45] CPRD	UK; N=27,557	-	196.6 (195.1, 198.3)‖	Oshagbemi (2017) [53]	UK; N=39,824	-	230 ± 260

Llanos (2018) [6] NHANES	USA; N=479	-	221 ± 10	Song (2017) [54] KOCOSS	Korea; N=467	166.5 (89.6–272.8)	-
Ortega (2018) [46]	*USA; N=11,329*		*297.6 ± 264.4*	Kobayashi (2016) [55]	Japan; N=220	-	212 ± 223
Shin (2018) [47] KOLD	*Korea; N=299*	-	*288.6 ± 344.6*	Suzuki (2016) [56] Hokkaido COPD Study	Japan; N=268	169 (94–261)	-
Turato (2018) [48]	*Spain; N=294*	-	*189.9*	Vedel-Krogh (2016) [57] CGPS	Denmark; N=7,225	180 (120–270)	-
Zeiger (2018) [49]	USA; N=7,245	-	194 ± 231[d]	Zeiger (2016) [58]	USA; N=901	-	259 ± 257
CONTROLS (non-asthma, non-COPD) (n=6 articles and n=6 populations)							
Landis (2018) [45] CPRD§§	UK; N=27,577	-	182.1 (180.7, 183.5)‖	Racine (2017) [59]‖‖[e]	Canada; N=237	100 (200)‡‡	-
Burte (2017) [13] EGEA2‖‖	France; N=362	-	149 ± 106	Vedel-Krogh (2017) [16] CGPS‖‖	Denmark; N=76,440	160 (110–240)	-
Oshagbemi (2017) [53]§§	UK; N=90,772	-	210 ± 350	Bouzigon (2012) [32] EGEA‖‖	France; N=783	130 (100–200)	-
GENERAL POPULATION (n=13 articles and n=13 populations)							
Bakrim (2018) [60]	*Morocco; N=14,965*	-	*124.7 ± 170.1*	Izuhara (2016) [67] Nagahama Study	Japan; N=9,804	-	155 ± 128
Dauchet (2018) [61] ELISABET (2011–2013)	France; N=1,506	139 (115)‡‡	-	Vedel-Krogh (2016) [57] CGPS	Denmark; N=81,668	170 (110–250)	-
Omuse (2018) [62]	Kenya; N=528	130	-	*Troussard (2014) [68]*	*France; N=32,919*	-	*200.6 ± 147.4*
Wongkrajang (2018) [63]	*Thailand; N=240*	-	*200.0 ± 157.9*	Ko (2013) [69]	Hong Kong, China; N=1,093	100 (1,300)‡‡	188 ± 196
Nerpin (2018) [64] NHANES	USA; N=7,753	-	200 ± 170	Malinovschi (2013) [70] NHANES	USA; N=12,408	200 (0–8,400)	-
Ozarda (2017) [65]	Turkey; N=3,363	140	-	Musk (2011) [71]	Australia; N=1,969	-	210
Giovannelli (2016) [66] ELISABET	France; N=1,579	-	163 (158, 168)‖				

*Entries in italics indicate publications for which data for the total population were calculated from the available published sub-group data (no data for the total population were originally reported)

†Unless otherwise indicated (footnotes a–d), data are baseline EOS counts

‡Arithmetic mean ± SE

§Median (range)

‖Geometric mean (95% CI)

**Data reported for the second entry are from the same publication but a different patient cohort (as indicated)

††Geometric mean (log10 SD)

‡‡Median (IQR)

§§Control population reported in the respective published study of COPD

‖‖Control population reported in the respective published study of asthma

[a]During the observation period (Jan 2003-Aug 2013; [b]Observed care patterns in the year prior to ICS/LABA and/or OCS; [c]Maximum count in two years prior to index date; [d]Index date (first EOS count up to 1 year after COPD diagnosis date); [e]Data for the respective asthma population were only available for subgroups that couldn't be combined, reported in Supplementary Results B

Abbreviations: %ile, percentile; BSAR, Belgian Severe Asthma Registry; BTS, British Thoracic Society; CGPS, Copenhagen General Population Study; CI, confidence interval; COBRA, COhort of BRonchial obstruction and Asthma; COPD, chronic obstructive pulmonary disease; COREA, Cohort for Reality and Evolution of Adult Asthma in Korea; CPRD, Clinical Practice Research Datalink; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points; EGEA, Epidemiological study on the Genetics and Environment of Asthma; ELISABET, Enquête Littoral Souffle Air Biologie Environnement survey; EOS, eosinophil; GEIRD, Gene Environment Interactions in Respiratory Diseases; ICS, inhaled corticosteroid; IQR, interquartile range; KOCOSS, Korean COPD Subtype Study; KOLD, Korean Obstructive Lung Disease; LABA, long-acting β_2-agonist; Nagahama, Nagahama Prospective Genome Cohort for Comprehensive Human Bioscience; NHANES, National Health and Nutrition Examination Surveys; OPCRD, Optimum Patient Care Research Database; RItA (acronym from the Italian words standing for Italian Registry of SUA); SAAS, Seinäjoki Adult Asthma Study; SANI, Severe Asthma Network in Italy; SARP, Severe Asthma Research Program; SD, standard deviation; SE, standard error; TENOR, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens; UK, United Kingdom; USA, United States of America

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