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

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Blood eosinophil (EOS) counts are of interest as asthma/COPD treatment–response biomarkers. This comprehensive review describes EOS distributions/ranges published in asthma/COPD, controls and the general population. https://bit.ly/3ph1G9M

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Abstract

Background The clinical context for using blood eosinophil (EOS) counts as treatment–response biomarkers in asthma and 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 (January 2008 to November 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 and exclusively paediatric participants.

Results Overall, 91 eligible studies were identified, most had total-population-level data available: asthma (39 studies), severe asthma (12 studies), COPD (23 studies), control (seven studies) and general populations (14 studies); some articles reported data for multiple populations. Reported EOS distributions were right-skewed (seven studies). Reported median EOS counts ranged from 157–280 cells·μL^{-1} (asthma, 22 studies); 200–400 cells·μL^{-1} (severe asthma, eight studies); 150–183 cells·μL^{-1} (COPD, six studies); and 100–160 cells·μL^{-1} (controls, three studies); and 100–200 cells·μL^{-1} (general populations, six studies). The meta-analysis showed that 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 COPD are chronic inflammatory airways diseases that result in limitations of lung airflow [1, 2]. However, the underlying disease mechanisms 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 eosinophil (EOS) counts to identify patients who are most at risk of asthma exacerbations, and who are most likely to benefit from

anti-interleukin (IL)5-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 a history of exacerbation [12]. Current Global Initiative for Chronic Obstructive Lung Disease guidelines recommend the use of blood EOS counts to identify patients with the greatest likelihood of treatment benefit with ICS [1].

However, several challenges 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.

Therefore, the clinical context for using blood EOS counts as a biomarker of treatment response in asthma and COPD 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 1 January 2008 and 12 November 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 S1 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 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 predefined 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 consulting 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 s (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^{-1} if not originally reported as such. For included articles that reported blood EOS data only for subgroups for mean, geometric mean or EOS categories, data were combined where possible to create a "total population" which 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 been published, which are discussed in context with our findings [23, 26].

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 [27], for which 5th and 95th percentiles were available). These quantiles can be used to calculate the corresponding standard deviation, 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 standard deviation (SD) was then estimated as follows:

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

$$Z \sim \mathrm{N}(0, 1)$$

then

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

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

$$X \sim \mathrm{N}(\mu, \sigma)$$

then

$$\begin{aligned} \mathrm{SD}(X) &= 1/0.67448 \times (\text{upper quartile}(X) - \mu) \\ &= 1/0.67448 \times (\mu - \text{lower quartile}(X)) \end{aligned}$$

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

$$\mathrm{SD}(X) = 1/0.67448 \times \sqrt{(((\text{upper quartile}(X) - \text{median}(X))^2 + (\text{median}(X) - \text{lower quartile}(X))^2)/2).}$$

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

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

The values of $\log_{10}$(median) and SE($\log_{10}$(median)) obtained by this method were used to perform a random-effects meta-analysis [28]. For the study by MÄKELÄ *et al*. [27], 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 an age range of 10–35 years [29–33]), 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, a total of 91 identified publications were available 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, five studies in asthma [34–38], two studies in severe asthma [39, 40], two studies in control populations without asthma or COPD [39, 40] and two studies in general populations [36, 41]

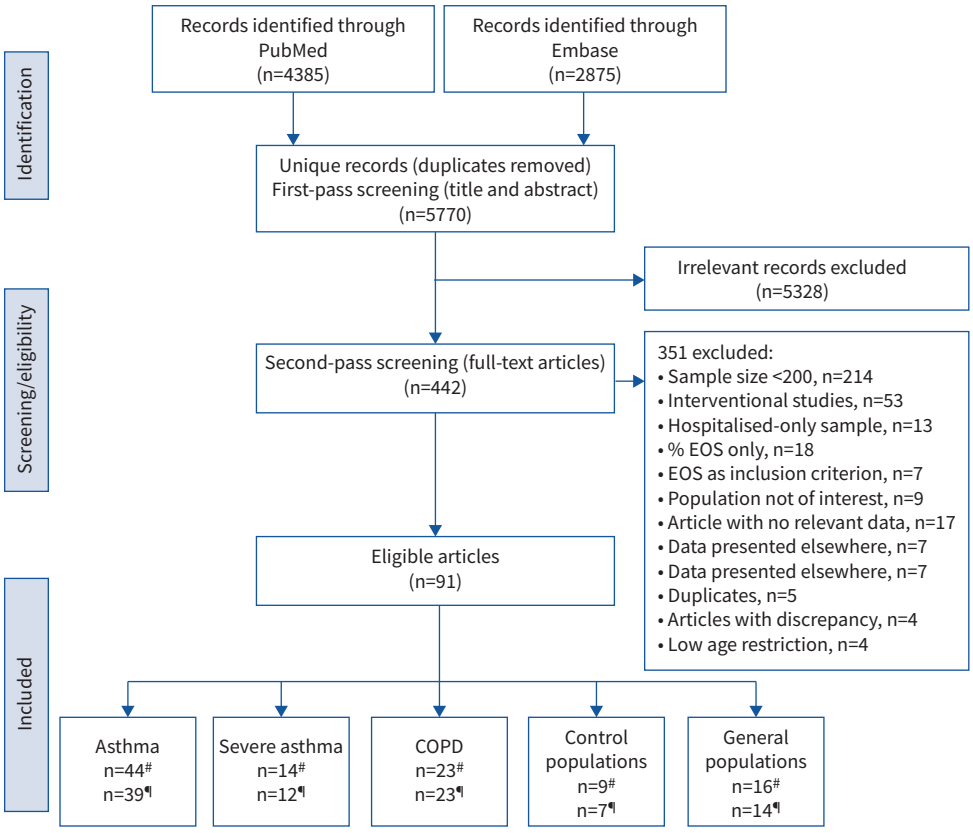


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of articles for inclusion, overall and by population type. EOS: eosinophil. #: the sum across the five categories (n=106) is greater than n=91 because some articles reported data for multiple relevant populations; ¶: studies where total population-level data were available; data for the studies presenting subgroup-level-only data are presented in supplementary results B.

TABLE 1 Patient/subject characteristics for total populations with asthma from included articles (39 articles and 40 populations)

First author (year), study or cohort name [reference]	Subjects	Age, years	Male, %	FEV_1, % predicted	ICS use, %[#]	Comorbidities, %[¶]
Amaral (2018) NHANES [60]	634	44.0 (31.0–57.0)	35.3		25	
Calciano (2018) GEIRD [61]	287	42.5±9.8	50.9	102.1±14.6[preBD]		
Çolak (2018) CGPS [41]	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) [62]+	463	26.3±8.55	51.62	83.6±17.99		
Lima-Matos (2018) [49]	452	35 (26–47)	23	87 (77–94)[postBD]		
Llanos (2018) NHANES [53]	1609	37±0.6	44	92.1±0.6[preBD]		T1/2D: 6.8; CVD: 5.5
Mäkelä (2018) [27]	4357	59.78 (19.31–84.40)[5–95th percentile]	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) [63]	212	50.5±13.2	48.58	88.9±19.8	74.1 (+LABA: 43.4)	
Seo (2018) [64]+	323	48.2±1.47	37.77	86.3±1.48		Atopy: 42.41
Teague (2018) SARP III [45]	213	44.5±14.6	33.3	92.2±15.5[postBD]		
Akiki (2017) EGEA II [57]	283	36.6±15.4	50.5	97.0±16.8	50.7 (n=280)[§]	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 [46]+	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[f]		Atopy: 68.0
Pola-Bibian (2017) [93]	831	57.3 (14–102)[range]	32.3			COPD: 13.7; CVD: 14
Pretolani (2017) COBRA [50]	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 [47]	4838	56 (47–66)	39	87 (73–98)	57	Allergy: 78
Zeiger (2017) [94]	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) [95]+	1144	47[mean]	29.16			T1/2D: 13.99; CVD: 5.94; malignancy: 6.38
de Groot (2016) [96]	491	51.8±13.0	39.3	96.6±18.2[postBD]	100[##]	NP±CRS: 19.3; atopy: 30.5
Nadif (2016) [58]+	716	41.6±13.94	50.28	95.15±19.38	48.32[¶¶]	
Tuomisto (2016) SAAS [65]	203	46±14	41.9	88 (77–99)[postBD]	8.0[++]; 76.4[§§]	
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[ff]	T1/2D: 19.9; NP±CRS: 4.3; atopy: 32.3; allergy: 28.8
Westerhof (2015) [66]	336	53±13	45	97±18[postBD]		NP±CRS: 19; atopy: 32
Agarwal (2014) [67]	296	36.2±13.6	52.6	74.5±4.03		atopy: 27
Lee (2014) [42]+	533		45.78	80.89±1.35		
Schleich (2014) Retrospective [51]	508	52 (19–88)	39.56	84±19	L/M/H: 14/ 27/28	NP±CRS: 22; AR: 58
Schleich (2014) Prospective [51]	250	50 (16–85)	39.6	82±21	L/M/H: 14/ 25/28	NP±CRS: 27; AR: 56
Tran (2014) NHANES [99]	1721	40±0.4[###]	37			
Ali (2013) [68]+	1075	38.0±15.63	60.56	86.04±19.84		
Amelink (2013) [100]	200	53.9±10.8	29.5	91.8±20.9[postBD]	41.5	NP±CRS: 37; atopy: 45
Hastie (2013) SARP [101]+	257	35.9±12.86	27.63	80.08±17.13[preBD]		
Park (2013) COREA [69]+	2067	49.7±15.79	46.27	80.2±21.44		
Bouzigon (2012) EGEA [48]	494	39.8±16.4	51	95.4±19.0	17.6/ 48.4[¶¶¶]	AR: 60.1

Continued

TABLE 1 Continued

First author (year), study or cohort name [reference]	Subjects	Age, years	Male, %	FEV_1, % predicted	ICS use, %[#]	Comorbidities, %[¶]
Matsunaga (2012) [70]	229	46.6±14.7	41.92	96.7±15.9	100.0	AR: 69.0; atopy: 76.9
Nadif (2009) French EGEA [59]	381	36.5±13.1	50.4	93.5±19.9	52.2[§]	

Data are presented as n, median (interquartile range (25th–75th percentile)) or mean±SD, unless otherwise stated. Empty cells indicate that data were not reported in the study/article. FEV_1: forced expiratory volume in 1 s; ICS: inhaled corticosteroid; NHANES, National Health and Nutrition Examination Survey; GEIRD: Gene–Environment Interactions in Respiratory Diseases; CGPS: Copenhagen General Population Study; CPRD: Clinical Practice Research Datalink; OPCRD: Optimum Patient Care Research Database; SARP: Severe Asthma Research Program; EGEA: Epidemiological study on the Genetics and Environment of Asthma; COBRA: Cohort of Bronchial Obstruction and Asthma; SAAS: Seinäjoki Adult Asthma Study; COREA: Cohort for Reality and Evolution of Adult Asthma in Korea; BD: bronchodilator; CVD: cardiovascular disease; NP: nasal polyps; CRS: chronic rhinosinusitis; AR: allergic rhinitis; T1/2D: type 1/2 diabetes; LABA: long-acting β_2-agonist; CHF: congestive heart failure; FA: food allergy; OSP: osteoporosis; HF: heart failure; IHD: ischaemic heart disease; L/M/H: low/medium or moderate/high dose; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist. [#]: data represent baseline values, unless otherwise indicated; [¶]: CVD excludes high blood pressure; atopy includes eczema; perennial AR includes perennial allergen sensitisation; [+]: publications for which data for the total population were calculated from the available published subgroup data (no data for the total population were originally reported); [§]: past 12 months; [f]: maximum value from four different procedures; [##]: all patients were receiving regular medium–high-dose ICS; [¶¶]: time of assessment not reported; [++]: at baseline; [§§]: at follow-up; [ff]: +LABA±LAMA: 34.1; +LTRA±LABA±LAMA: 4.8; [###]: mean±SE; [¶¶¶]: past 3/12 months.

only reported median EOS count data from subgroups and not the total population, which therefore could not be combined to create total population-level data for these categories (subgroup data are thus presented separately: supplementary results B). However, total population-level data were available for the COPD and control populations for two of these studies [34, 41]. Details of the eligible articles, including study inclusion criteria, for which total population data could be calculated based on available data are reported in supplementary table S2 and an in-depth description of the studies is provided in 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 (37 studies/46 populations), North America (20 studies/23 populations) and Asia (18 studies/18 populations), with one study (two populations) in South America, two studies in Oceania and three studies in Africa; two studies included more than one region [43, 44] and 14 studies included multiple populations [41, 43, 45–53, 55, 56]. 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 (one asthma study also reported a severe asthma cohort [45]); 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 seven asthma studies [41, 46–48, 57–59]; diagnoses were confirmed using lung function testing as stated in 23 asthma studies [27, 36, 41, 42, 44, 46–51, 57–70], eight severe asthma studies [45, 49–51, 71–74] and 18 COPD studies [41, 43, 44, 52–55, 75–87].

Population characteristics

Characteristics for the participants in analysed studies where total population-level data were available are reported in tables 1–4.

Asthma

The range across the 39 asthma studies (table 1) for average age was 26.3–60.2 years; 23.0–60.6% were male. Across the studies the range of average FEV_1 was 74.5–102.1% predicted and the range of FEV_1/FVC ratios was 0.68–0.93; two studies specifically included "mild–moderate" asthma [49, 81], two studies included "mild–severe" asthma [50, 95], one study included "moderate–severe" asthma [89], one study included "non-severe" asthma [45] 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; two cohorts in one study [51]) and a history of atopy/eczema (16 studies).

Severe asthma

In the 12 severe asthma studies (table 2), 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 average FEV_1/FVC ratios was 0.63–0.87. Nine studies

TABLE 2 Patient/subject characteristics for total populations with severe asthma from included articles (12 articles and 12 populations)

First author (year), study or cohort name [reference]	Subjects	Age, years	Male, %	FEV_1, % predicted	ICS use, %[#]	Comorbidities, %[¶]
Heffler (2019) SANI [102]	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
Haughney (2018) [71]	884	54.7±15.9	31.3		24.9[§] (+LABA: 96.4[§])	COPD: 32.5; T1/2D: 13.9; CVD: 12.2; OSP: 4.3; depression: 5.7; NP±CRS: 1.0
Husereau (2018) [103]	212[f]	43±16	42		+LABA: 100[##]	T1/2D: 7; AR: 9; atopy: 7; anxiety: 9; depression: 3
Lima-Matos (2018) [49]	544	52 (43–61)	19	70 (58–81)[postBD]	38	
Maio (2018) RItA [72]	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 [45]	313	49.7±12.8	32.9	77.9±19.7[max. postBD]		
Chipps (2018) TENOR II [104]	341	57.8±16.3	34.6	78.9±20.6[¶¶, 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 [50][+]	613	51.1±14.72	34.75	74.13±33.00[preBD]	98.84[++]	Atopy: 86.38; AR: 65.84; NP±CRS: 30.92; CVD: 20.59; FA: 14.80
Zeiger (2017) [105]	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) [73]	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 [74]	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 [106]	350	55±0.8	43	68±1.2		Atopy: 70; CRS: 49; overweight: 47; GORD: 36; NP±CRS: 19; depression: 19; bronchiectasis: 16

Data are presented as n, mean±SD or median (interquartile range (25th–75th percentile)), unless otherwise stated. Empty cells indicate that data were not reported in the study/article. FEV_1: forced expiratory volume in 1 s; ICS: inhaled corticosteroid; SANI: Severe Asthma Network in Italy; RItA: the Italian severe/uncontrolled asthma registry; SARP: Severe Asthma Research Program; TENOR: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens; COBRA: Cohort of Bronchial Obstruction and Asthma; BTS: British Thoracic Society; BSAR: Belgian Severe Asthma Registry; LABA: long-acting β_2-agonist; T1/2D: type 1/2 diabetes; CVD: cardiovascular disease; OSP: osteoporosis; NP: nasal polyps; CRS: chronic rhinosinusitis; AR: allergic rhinitis; FA: food allergy; BD: bronchodilator; max: maximum; CHF: congestive heart failure; CAD: coronary artery disease; OHD: other heart disease; GORD: gastro-oesophageal reflux disease. [#]: data represent baseline values, unless otherwise indicated; [¶]: CVD excludes high blood pressure; atopy includes eczema; perennial AR includes perennial allergen sensitisation; [+]: publications for which data for the total population were calculated from the available published subgroup data (no data for the total population were originally reported); [§]: at least one prescription 2 years prior to index date; [f]: eosinophil data available for n=212; [##]: at index date; [¶¶]: Global Lung Function Initiative estimates of percentage predicted pre-BD and post-BD FEV_1; [++]: time of assessment not reported; [§§]: derived values.

reported OCS use by 8–64% of participants; nine studies reported ICS use by 25–100% of participants. Recently approved biologic therapies were in use for severe asthma: anti-IgE in six studies (2.5–64.1% of participants [50, 72, 73, 102, 104, 106]) and anti-IL5 in one study (11.2% of participants [102]), while undefined "specific immunotherapy" was reported by two studies (0.6–4.1% of participants [72, 106]). The most commonly reported comorbidities for severe asthma were nasal polyps (nine studies), a history of atopy (seven studies) and allergic rhinitis (seven studies).

COPD

For the 23 COPD studies (table 3), the range of average age was 54.1–75.0 years, and 37.4–97.3% of participants were male. The range of average FEV_1 was 31–81% pred 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 (seven studies) and diabetes were the most commonly reported comorbidities (six studies).

Control and general populations

The control populations (without asthma in asthma studies or COPD in COPD studies) from seven studies (table 4) had a range of average ages of 46.6–71.1 years; 45–58.2% were male. The range of average FEV_1 was 95–107% pred; the average FEV_1/FVC ratio was reported by two studies (0.78 in both). Five studies

TABLE 3 Patient/subject characteristics for total populations with COPD from included articles (23 articles and 24 populations)

First author (year), study or cohort name [reference]	Subjects	Age, years	Male, %	FEV_1, % predicted	ICS use, %[#]	Comorbidities, %[¶]
Chalmers (2018) [75][+]	4009	67.8±10.30	60.48	59.26±19.00	43.53[§]	Asthma history: 15.33; T1/2D: 15.23; CVD: 10.08; OSP: 12.8
Çolak (2018) CGPS [41]	404	68 (60–75)	54	81 (69–94)		Asthma history: 17; allergy: 27
Greulich (2018) COSYCONET [76]	334	64.37±8.33	63.2	55.5±17.97	57.8	Asthma history: 20.1
Halper-Stromberg (2018) COPDGene [43]	4558	65.5±8.7[f]	50	78.3±24.9[f]	24	
Halper-Stromberg (2018) ECLIPSE [43]	1741	61.9±7.9[f]	64	55.0±26.1[f]	59	
Landis (2018) CPRD [52]	27 557	71.1±10.6	51.5		68.0[##]	Asthma history: 35.7
Llanos (2018) NHANES [53]	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 [77][+]	299	66.8±7.36	97.32	48.07±15.30	40.47[§]	Asthma history: 28.09
Turato (2018) [78][+]	294	61.8±8.21		68.0±19.76[postBD]	58.84[§]	
Zeiger (2018) [79]	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) [80]	1066	67 (60–75)	60	31 (23–43) (n=345)		
Casanova (2017) CHAIN/BODE [44][+]	732	66.3±8.94	82.51	59.85±20.21	61.34[§]	
Hastie (2017) SPIROMICS [81][+]	2499		54.46	68.42 (mean)[preBD]	34.97[§]	Asthma history: 20.5
Inoue (2017) [84]	1008	73.5±8.3	93.0	56.7±21.1	7.4 (+LABA: 40.1)	
Kerkhof (2017) [82]	8318	70±10	56.4		49.1	
Kim (2017) KOLD [83]	307	75 (69–79)	97.1	52.9±16.1[postBD]		
Oshagbemi (2017) [56]	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 [85]	467	69.5±7.4	95.9	55.5±18.0	+LABA: 53.6	
DiSantostefano (2016) NHANES (2007–2010) [54]	948	[¶¶]	59.7			Asthma history: 18.5; asthma: 11.7
Kobayashi (2016) [86]	220	75.0±7.0	92.3	61.4±22.1	36.8	AR: 2.3
Suzuki (2016) Hokkaido COPD [87]	268	69±8	94	65±22[postBD]		CVD: 22; IHD: 7; T1/2D: 5
Vedel-Krogh (2016) CGPS [55]	7225	64 (54–72)	50	78 (64–90)	7	T1/2D: 2; CVD: 9; allergy: 20
Zeiger (2016) [108]	901	54.1±8.8	37.4		89	Asthma: 79.5; AR: 35.8; NP±CRS: 4.2; atopy: 1.3

Data are presented as n, mean±SD or median (interquartile range (25th–75th percentile)), unless otherwise stated. Empty cells indicate that data were not reported in the study/article. FEV_1: forced expiratory volume in 1 s; ICS: inhaled corticosteroid; CGPS: Copenhagen General Population Study; COSYCONET: COPD and Systemic Consequences – Comorbidities Network; ECLIPSE: Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points; CPRD: Clinical Practice Research Datalink; NHANES: National Health and Nutrition Examination Surveys; KOLD: Korean Obstructive Lung Disease; CHAIN: COPD History Assessment in Spain; BODE: Body mass index, degree of airflow Obstruction, functional Dyspnoea and Exercise capacity; SPIROMICS: Subpopulations and Intermediate Outcome Measures in COPD Study; KOCOSS: Korean COPD Subtype Study; T1/2D: type 1/2 diabetes; CVD: cardiovascular disease; OSP: osteoporosis; BD: bronchodilator; AR: allergic rhinitis; CHF: congestive heart failure; CAD: coronary artery disease; LABA: long-acting β_2-agonist; IHD: ischaemic heart disease; NP: nasal polyps; CRS: chronic rhinosinusitis. [#]: data represent baseline values, unless otherwise indicated; [¶]: CVD excludes high blood pressure; atopy includes eczema; perennial AR includes perennial allergen sensitisation; [+]: publications for which data for the total population were calculated from the available published subgroup data (no data for the total population were originally reported); [§]: time of assessment not reported; [f]: mean±SE; [##]: follow-up at 12 months; [¶¶]: 220 (32.3%) were in the age group 50–59 years.

reported ICS use (three studies reported ICS use by 1.4–3.5% of the asthma/COPD control populations [47, 48, 56]; one COPD study reported ICS use by 9.3% of the control population [52] and one asthma study reported ICS use by 27.4% of the control population [34]). In these studies, asthma history was reported in 10.2% and 7.6% of the control population [34, 52]. None reported OCS use and the most commonly reported comorbidities were allergic rhinitis/hay fever (two studies) and asthma history (three studies).

The 14 general population studies (table 4) had a range of average ages of 28–58 years; 33–59% of participants were male (one study reported 33% males [116]; the other studies ranged from 45% to 59%

TABLE 4 Patient/subject characteristics for total populations (control (seven articles and seven populations) and general population (14 articles and 14 populations)) from included articles

First author (year), study or cohort name [reference]	Subjects	Age, years	Male, %	FEV_1, % predicted	ICS use, %[#]	Comorbidities, %[¶]
Controls						
Landis (2018) CPRD[+] [52]	27557	71.1±10.6	51.5		9.3[¶¶]	Asthma history: 10.2
Burte (2017) EGEA2[§] [46]	362	46.8±16.3	50	107 (mean)		AR/hay fever: 5.5/10.8; eczema: 22.7
Oshagbemi (2017)[+] [56]	90772	69.9±10.6	51.1		1.4	CVD: 28.5; OSP: 5.2; anxiety: 12.2; malignancy: 15.9
Racine (2017)[§,f] [34]	237	50.2±10.9	58.2	100.6±14.4	27.4	Asthma history: 7.6; atopy: 65.0
Vedel-Krogh (2017) CGPS[§] [47]	76440	58 (48–67)	45	97 (87–106)	2	Allergy: 25
DiSantostefano (2016) NHANES (2007–2010)[+] [54]	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[§§]	AR: 22.1
General population						
Bakrim (2018) [109][##]	14965	30.4±9.72	52.99			
Dauchet (2018) ELISABET (2011–2013) [110]	1506	53.5±7.2	44.8			
Nerpin (2018) NHANES [111]	7753	47.5 (median)	51	97.0±15.6		Asthma: 6.5
Omuse (2018) [112]	528	39.0 (20.0–63.0)[2.5th–97.5th percentile]	48.2			
Wongkrajang (2018) [113][##]	240		50.00			
Ozarda (2017) [114]	3363	[ff]	47.9			
Giovannelli (2016) ELISABET [115]	1579	53.3±7.3	48.5	1.04±0.18	1.1	Asthma: 7.3; atopy: 32
Izuhara (2016) Nagahama [116]	9804	53.5±13.4	33			Asthma: 4; COPD: 1; AR: 35
Vedel-Krogh (2016) CGPS [55]	81668	58 (48–67)	45	96 (86–106)	5	T1/2D: 2; CVD: 6; allergy: 28
Troussard (2014) [117][##]	32919		58.91			
Ko (2013) [118]	1093	47.3±16.6	47.2	106.79 ±13.87[postBD]		Atopy positive: 59
Malinovschi (2013) NHANES [29]	12408	36 (6–80)	51		4.0[###]	Asthma: 8.3; hay fever: 13.7
Musk (2011) [119]	1969	54±17	49.4	96.3 (mean)		Asthma: 18
Karita (2009) [120]	2105	28 (18–59)	51			

Data are presented as n, mean±SD or median (interquartile range (25th–75th percentile)), unless otherwise stated. Empty cells indicate that data were not reported in the study/article. FEV_1: forced expiratory volume in 1 s; ICS: inhaled corticosteroid; CPRD: Clinical Practice Research Datalink; EGEA: Epidemiological study on the Genetics and Environment of Asthma; CGPS: Copenhagen General Population Study; NHANES: National Health and Nutrition Examination Surveys; ELISABET: Investigation of Air and Breath in a Coastal Biological Environment; Nagahama: Nagahama Prospective Genome Cohort for Comprehensive Human Bioscience; AR: allergic rhinitis; CVD: cardiovascular disease; OSP: osteoporosis; T1/2D: type 1/2 diabetes; BD: bronchodilator. [#]: data represent baseline values, unless otherwise indicated; [¶]: CVD excludes high blood pressure; atopy includes eczema; perennial AR includes perennial allergen sensitisation; [+]: control population reported in the respective published study of COPD; [§]: control population reported in the respective published study of asthma; [f]: data for the respective asthma population were only available for subgroups that couldn't be combined, reported in supplementary results B; [##]: publications for which data for the total population were calculated from the available published subgroup data (no data for the total population were originally reported); [¶¶]: follow-up at 12 months; [++]: 1090 (40.9%) were in the age group 40–49 years; [§§]: past 3/12 months; [ff]: 2914 (86.6%) were aged 20–59 years; [###]: use of ICS or oral corticosteroid in the past 2 days.

male). The range of average FEV_1 was 96–107% pred, where available (five studies), and the range of FEV_1/FVC ratios was 0.77–0.97 (five studies). ICS use was reported by two studies (by 1.1–5% of participants [55, 115]) and one reported ICS or OCS use in the past 2 days (by 4% of participants [29]); the most frequently reported comorbidities were current asthma (five studies) and allergic rhinitis/hay fever (two studies).

Distribution of blood EOS

Seven studies that describe the distribution of blood EOS counts were identified [41, 44, 47, 52, 54, 82, 87]; 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 [47, 54]. Each histogram represents the results of a single representative study. The highest blood EOS counts reached $\geqslant$1000 cells·μL^{-1} in a small proportion of individuals with asthma [47] (figure 2a), COPD [54, 79, 83, 84] (figure 2b) and control populations [41, 44, 47, 52, 54] (figure 2c). No distribution data were reported for severe asthma during this review period.

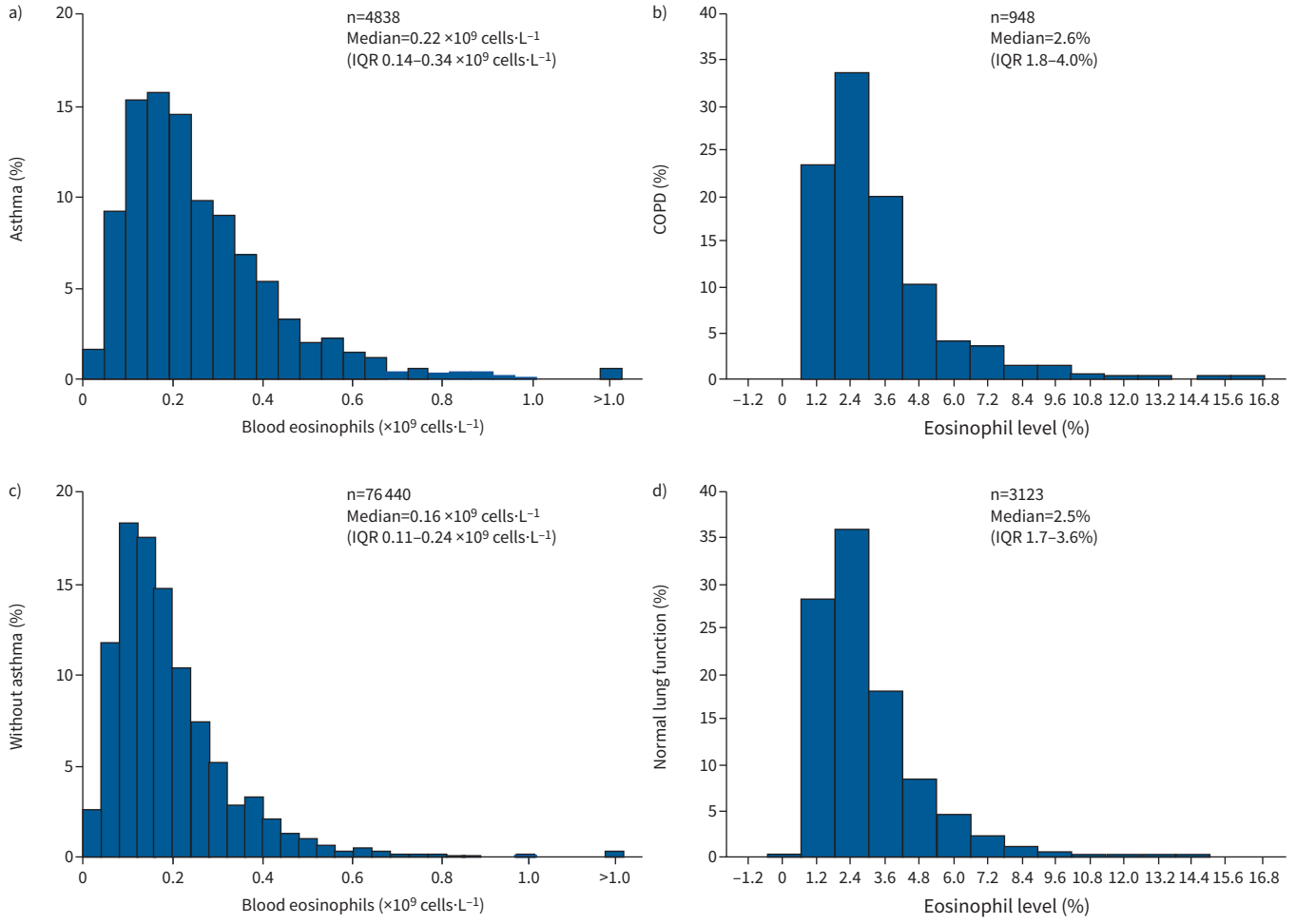


FIGURE 2 Blood eosinophil distributions in a) asthma, b) COPD and c) control and d) general populations. IQR: interquartile range. a, c) Reproduced from [47] with permission. b, d) Reproduced and modified from [54] with permission.

In the control population with healthy lung function of a United States population-based COPD cohort, ∼28% and ∼35% of individuals had blood EOS levels of up to 1.2% and 2.4%, respectively [54]. Blood EOS distributions for the entire Copenhagen General Population Study followed a similar trend to the control populations [47]. Although the corresponding percentage of blood EOS was not reported, correlation analyses found that blood EOS counts of 100, 150 and 300 cells·μL^{-1} were equivalent to ∼1.3%, ∼1.9% and ∼3.8%, respectively, of total white blood cells in the study population [52].

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 S3 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 subgroup 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 described earlier. 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^{-1} (figure 3, solid vertical line) 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 ∼500 cells·μL^{-1} (figure 3, dashed vertical line) [121–123].

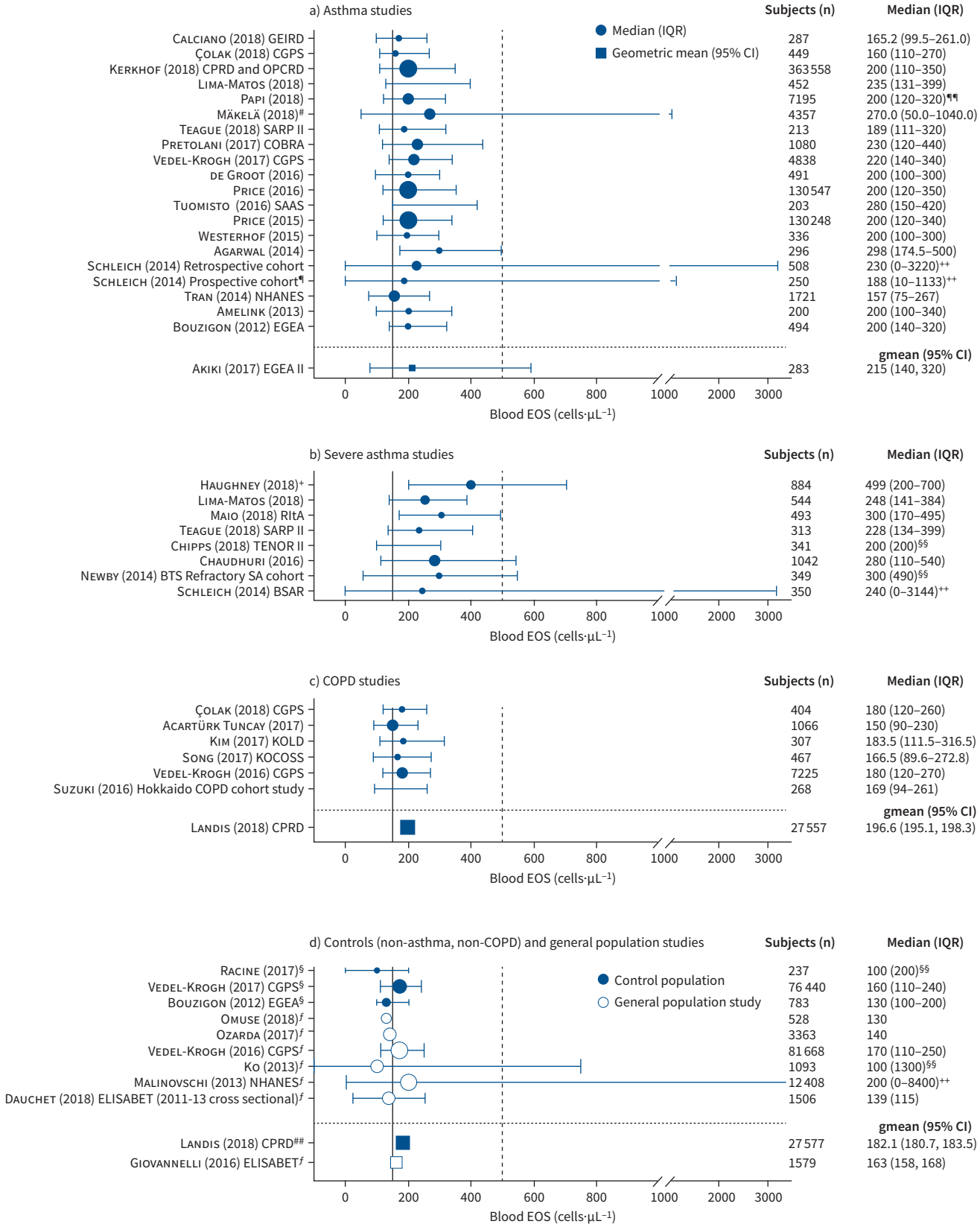


FIGURE 3 Forest plots of median (interquartile range (IQR) or range) and geometric mean (gmean) (95% CI) blood eosinophil (EOS) counts for each of the five population types: a) asthma, b) severe asthma, c) COPD and d) controls and general populations. Symbols are presented according to study size, in ascending order: n<500; n⩾500–<1000; n=⩾1000–<10 000; n⩾10 000–<100 000; 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^{-1}, while dashed lines represent the upper limit of normal blood EOS levels, generally considered to be ~500 cells·μL^{-1} [119–121]. Unless otherwise indicated, all studies measured the blood EOS values at baseline. GEIRD: Gene Environment Interactions in Respiratory Diseases; CGPS: Copenhagen General Population Study; CPRD: Clinical Practice Research Datalink; OPCRD: Optimum Patient Care Research Database; SARP: Severe Asthma Research Program; COBRA: Cohort of Bronchial Obstruction and Asthma; SAAS: Seinäjoki Adult Asthma Study; NHANES: National Health and Nutrition Examination Surveys; EGEA: Epidemiological Study on the Genetics and Environment of Asthma; RItA: the Italian severe/uncontrolled asthma registry; TENOR: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens; BTS: British Thoracic Society; SA: severe asthma; BSAR: Belgian Severe Asthma Registry; KOLD: Korean Obstructive Lung Disease; KOCOSS: Korean COPD Subtype Study; ELISABET: Enquête Littoral Souffle Air Biologie Environnement survey. [#]: blood EOS values not measured at baseline, but during the observation period (January 2003–August 2013); [¶]: data from a separate patient cohort (as indicated); [+]: maximum count in 2 years prior to index date; [§]: control population reported in the respective published study of asthma; [ƒ]: general population study; [##]: control population reported in the respective published study of COPD; [¶¶]: median (5–95th percentile); [++]: median (range); [§§]: where IQR was reported as one value, the range could not be plotted due to unknown skew.

Asthma

Of the 34 asthma studies with data on absolute blood EOS counts, 20 reported median counts in the range 157–298 cells·μL^{-1} and one reported a geometric mean count of 215 cells·μL^{-1} (13 studies reported arithmetic mean counts of 233–507.9 cells·μL^{-1}; one study reported both median and arithmetic mean counts [99]). Four studies where >20% of the study population used OCS at baseline showed similar blood EOS counts (median 200 cells·μL^{-1} [89, 100], geometric mean 215 cells·μL^{-1} [92], arithmetic mean 263 cells·μL^{-1} [94]). The meta-analysis of medians reported significant heterogeneity (Chi-squared=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^{-1}. Three asthma studies reported the proportion of patients with blood EOS counts ⩾150 cells·μL^{-1}, ranging from 61.1% to 100% [53, 94, 124].

Severe asthma

For severe asthma, eight studies reported median blood EOS counts in the range 200–400 cells·μL^{-1} and no geometric mean data were reported (four studies reported arithmetic means of 200–536.7 cells·μL^{-1}; one study reported both median and arithmetic mean counts [104]). All studies reported data from the total severe asthma population, except for one study that reported median (interquartile range (IQR)) values of 240 (130–460) cells·μL^{-1} for GINA category 4 and 280 (100–540) cells·μL^{-1} for GINA category 5 [50]. The meta-analysis of medians reported significant heterogeneity (Chi-squared=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^{-1}. One severe asthma study reported the proportion of patients with blood EOS counts ⩾150 cells·μL^{-1} (79.8%) [102].

COPD

In COPD, six studies reported median counts in the range 150–183.5 cells·μL^{-1} and one reported a geometric mean count of 196.6 cells·μL^{-1} [52] (11 studies reported arithmetic mean counts of 189.9–297.6 cells·μL^{-1}). The meta-analysis of medians reported significant heterogeneity (Chi-squared=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^{-1}. Five COPD studies reported the proportion of patients with blood EOS counts ⩾150 cells·μL^{-1}, ranging from 18% to 72.7% [52, 53, 78, 79, 107].

Control and general populations

Of the six studies with a control population (without asthma or COPD, depending on the study) that included data on absolute blood EOS counts, three reported median counts 100–160 cells·μL^{-1} and one reported a geometric mean count of 182.1 cells·μL^{-1} [52] (two studies reported arithmetic mean counts of 149 cells·μL^{-1} and 210 cells·μL^{-1}).

In the 13 general population studies with data on absolute blood EOS counts, six reported median counts generally <150 cells·μL^{-1}, although one large study was above this threshold at 170 cells·μL^{-1} [55], and the National Health and Nutrition Examination Survey's general population recorded a median count of 200 cells·μL^{-1} [29]. One study reported a geometric mean count of 163 cells·μL^{-1} (seven studies reported arithmetic mean counts of 124.7–200.6 cells·μL^{-1}).

The meta-analysis of medians reported significant heterogeneity (Chi-squared=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^{-1}.

Factors associated with blood EOS count

Çolak *et al*. [41] reported that the following factors were associated with a blood EOS count ⩾300 cells·μL^{-1}: 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 <80% and/or below lower limit of normal (LLN); FEV_1/FVC ratio <0.70 and/or below LLN [41]. These factors are illustrated in figure 4a. Conversely, familial predisposition of COPD was associated with a lower blood EOS count [41]. 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^{-1} for defining higher blood EOS counts. The Lung, hEart, sociAl, boDy (LEAD) study, a large Austrian general population study of 11 042 participants, found that 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^{-1} 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]. In addition, increasing numbers of concomitant associated factors were 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^{-1} (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^{-1}, increasing to 153 cells·μL^{-1} with one risk factor, and further increasing to 190–192 cells·μL^{-1} with two to four 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

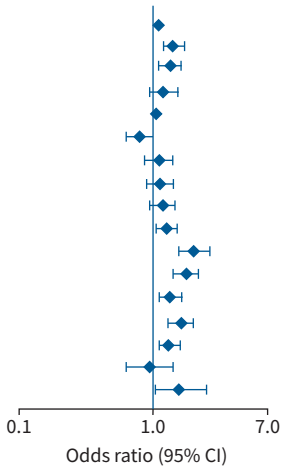
This comprehensive literature review included 91 observational studies that reported baseline EOS counts in asthma, severe asthma, COPD, control (non-asthma/COPD) and general populations. Despite the wide range of treatment options available for asthma and COPD, a substantial unmet clinical need remains. 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.

91 publications were included in the literature review, covering patient, control and general populations; sample sizes ranged from 200 to 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^{-1} and 30–395 cells·μL^{-1} 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^{-1} and 5th–95th percentile was 50–508 cells·μL^{-1} [26].

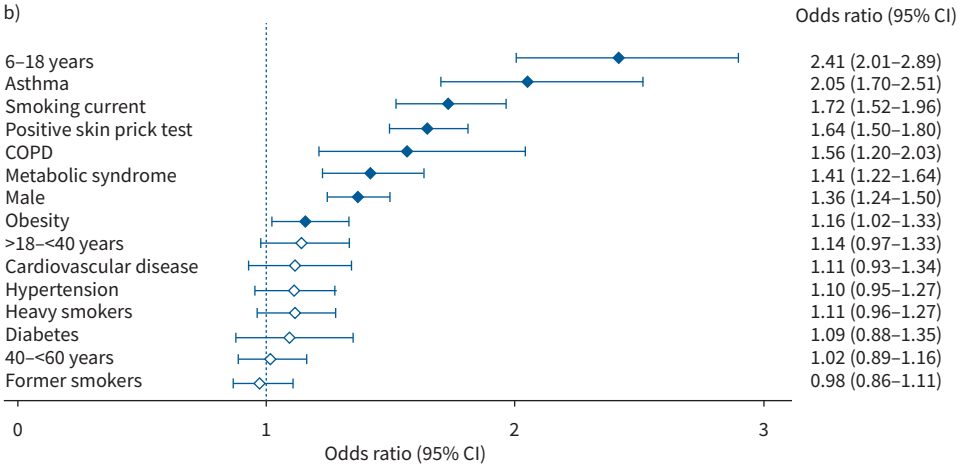
a)

Blood eosinophil count ≥300 cells·μL^{-1}

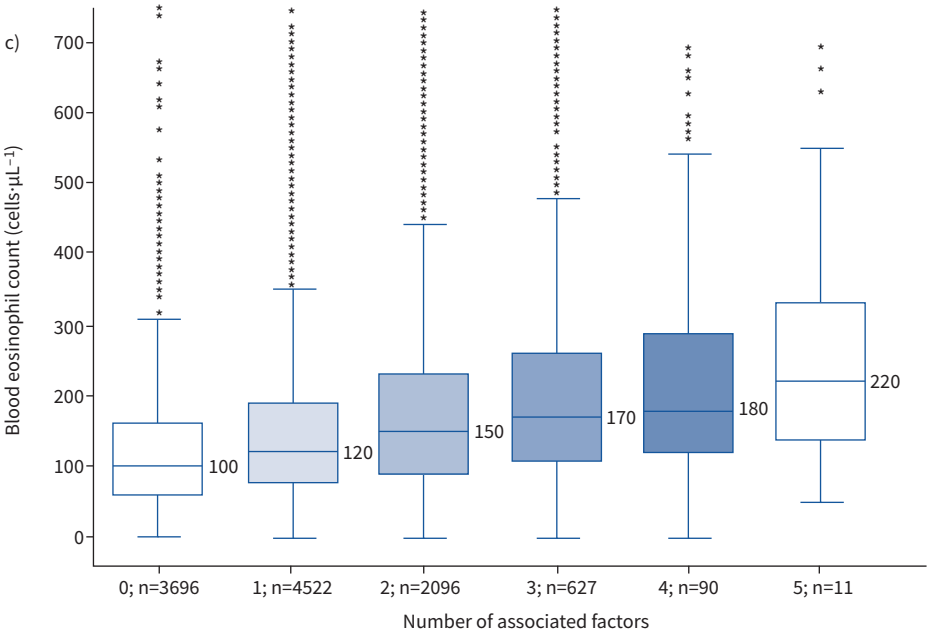
	Subjects n	Odds ratio (95% CI)	p-value
Age (per 10 years higher)	751	1.09 (1.03–1.16)	0.005
Sex (males *versus* females)	751	1.41 (1.20–1.65)	2×10^{-5}
BMI (per 10 kg·m^{-2} higher)	751	1.33 (1.12–1.58)	0.001
Current smoking	751	1.20 (0.96–1.50)	0.10
Smoking history (per 10 pack-years higher)	751	1.05 (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)	3×10^{-8}
FEV_1 % pred <LLN	751	1.76 (1.43–2.17)	8×10^{-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)	2×10^{-8}
FEV_1/FVC <0.70	751	1.32 (1.11–1.56)	0.001
Post-bronchodilator FEV_1/FVC <0.70	150	0.93 (0.64–1.37)	0.73
Reversibility	150	1.57 (0.99–2.48)	0.06



b)



c)



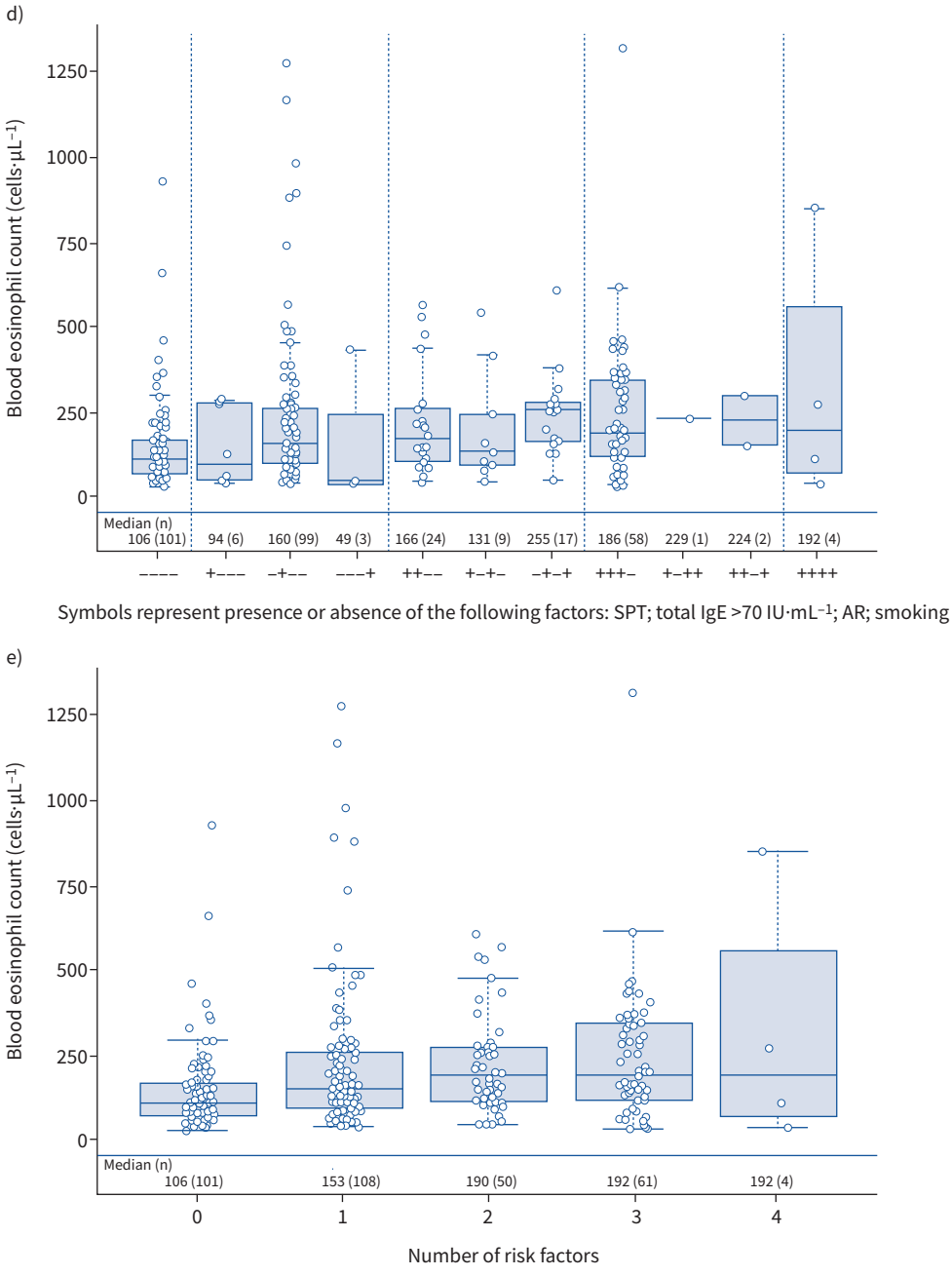


FIGURE 4 Blood eosinophil (EOS) levels and risk factors of interest for the general population reported in a) the Copenhagen General Population Study; b, c) the Lung, Heart, Social, Body (LEAD) study; and d, e) the non-asthmatic population reported in the Program for Control of Asthma in Bahia (ProAR) study. a) Clinical attributes associated with increased blood eosinophil count (⩾300 cells·µL^{-1}). Reversibility was defined as forced expiratory volume in 1 s (FEV_1) reversibility of ⩾12% and ⩾200 mL. Logistic regression models were used. Estimates are unadjusted. p-values were from Wald's test. Reproduced with permission from [41]. b, c) Reproduced with permission [23]. c, d) Reproduced with permission from [26]. BMI: body mass index; LLN: lower limit of normal; FVC: forced vital capacity; SPT: skin-prick test; AR: allergic rhinitis.

The right-skewed nature of EOS distributions was particularly relevant for the studies in control and general populations we identified; only six studies were found, of which three reported IQR, and none reported 95% confidence interval. For instance, one general population study reported a blood EOS range of 0–8400 cells·µL^{-1} [29]. Furthermore, many studies reported arithmetic mean EOS counts and therefore

were 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 to 182 cells·μL^{-1}. Similarly, studies examining general population cohorts reported median/geometric mean blood EOS counts ranging from 100 to 200 cells·μL^{-1}. The meta-analysis for the three included studies (two asthma control populations and one general population) reported a median (95% CI) of 157.0 (151.6–162.5) cells·μL^{-1}. 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 [125, 126], 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 aged <18 years, only two studies reported age ranges that included <18 years (14–102 years [93]; 16–85 years [106]). A median blood EOS count was only available for the latter of these studies (188 cells·μL^{-1} [106]), lower than the median counts ⩾200 cells·μL^{-1} 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^{-1}. Of the nine asthma studies that had a higher proportion of males than females, four reported median/geometric mean blood EOS counts (165–298 cells·μL^{-1} [48, 57, 61, 67]); the range of median/geometric mean counts in the other asthma studies was similar (157–280 cells·μL^{-1}). All severe asthma studies had a higher proportion of females than males and reported median EOS counts >200 cells·μL^{-1}. The meta-analysis of the five eligible severe asthma studies reported a median (95% CI) of 285.7 (234.8–347.7) cells·μL^{-1}; the highest estimate calculated among the meta-analyses. For COPD studies (n=23), all median blood EOS levels were ⩾150 cells·μL^{-1} and <200 cells·μL^{-1}; two out of the 23 COPD studies had a higher proportion of females than males [107, 108]; however, neither of these reported median/geometric mean blood EOS counts, precluding any interpretation of sex on EOS levels. For the six eligible COPD studies, a median (95% CI) of 171.0 (159.1–183.9) cells·μL^{-1} was reported.

In terms of ethnicity, existing studies report higher blood EOS counts in White and Hispanic populations *versus* Black and non-Hispanic populations [52, 127]. 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 [128]. In our review, obtaining data from Asian countries was difficult due to the limited number of studies. For asthma, two studies were conducted in India [62, 67], three in Korea [42, 64, 69] and two in Japan [70, 92]. There were no severe asthma populations from Asia in this review. For the COPD studies, three were from Korea [77, 83, 85] and three were from Japan [84, 86, 87]. For the general population analysis, one study was carried out in Japan [116], one in Thailand [113] and one in China [118]. 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^{-1}, 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^{-1} [52, 53, 94, 102, 107, 124], 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.* [129] 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^{-1}).

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 [130, 131]. Similarly, in asthma, exacerbations are more frequent in patients with high counts (>400 cells·μL^{-1}) than those with counts below this threshold [93, 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 [131]. 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 [132]. Smoking is thought to be a potential confounder for blood EOS count in COPD [1]; however, Pedersen *et al*. [133] 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 Mendelian randomisation approach in the Copenhagen General Population Study. Additionally, with regards to the link between obesity and blood EOS count, Peerboom *et al*. [134] did not find an association between BMI and blood EOS count in a cohort of 1217 patients with asthma. More recently, Esteban-Gorgojo *et al*. [135] 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). In addition, they suggest stratifying data by sex in future studies due to observable differences in certain characteristics between males and females [135]. 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 [136].

This comprehensive literature review combined data from various subpopulations 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 were utilised add weight to the conclusions of this review and reduce 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 [47] *versus* figure 2b and d [48]. 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 [137], described very specific populations (*e.g.* male firefighters in New York at the time of 9/11 [138]), 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 its inclusion as part of the study. In severe asthma, six studies reported that a proportion of patients were receiving biologic therapies (anti-IgE, anti-IL5 or undisclosed "specific immunotherapy") [50, 72, 73, 102, 106, 107], which may have influenced their blood EOS counts, although the median counts in these studies (200–300 cells·μL^{-1}) were within the overall range of median counts reported in severe asthma (200–400 cells·μL^{-1}). 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^{-1} [89, 92, 100]) and severe asthma (228–300 cells·μL^{-1} [45, 72–74]) were within the

reported overall ranges of median/geometric means in asthma (157–298 cells·μL^{-1}) and severe asthma (200–400 cells·μL^{-1}).

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.

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