# Supplementary Material

**CONTENTS**

## 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 S2.

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 S1. 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 keywords | ((("general population") OR healthy volunteers[MeSH Terms])) AND ((((Eosinophils[MeSH Terms]) OR eosinop*)) AND blood) | 103 |
| 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 S2. 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]<br>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]<br>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]<br>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]*<br>*SARP* | *USA* | *Mild or moderate asthma* |
| *Park (2013) [36]*<br>*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]<br>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]<br>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]<br>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]<br>RItA | Italy | Severe/uncontrolled asthma according to the WHO Consultation on Severe Asthma |
| Teague (2018) [12]<br>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]<br>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]*<br>*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]<br>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]<br>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]<br>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]<br>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]<br>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]<br>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]<br>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]*<br>*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]*<br>*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]*<br>*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]<br>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]<br>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]<br>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]<br>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]<br>CGPS | Denmark | $FEV_1/FVC$ <LLN; $FEV_1/FVC$ <70%; no self-reported asthma |

| | | |
|---|---|---|
| Zeiger (2016) [71]<br>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]<br>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]<br>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]<br>CGPS§ | Denmark | Aged 20–100 years were randomly selected from the general population for the CGPS |
| DiSantostefano (2016) [68]<br>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]<br>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]<br>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]<br>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]<br>ELISABET | France | Aged 40–64 years; resident in Dunkirk or the Dunkirk urban area for ≥5 years |
| Izuhara (2016) [81]<br>Nagahama Study | Japan | Citizens in Nagahama City in Japan; no current serious diseases, were able to live independently |
| Vedel-Krogh (2016) [70]<br>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]<br>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 S3. 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 $\beta_2$-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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