EUROPEAN RESPIRATORY journal

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Blood eosinophil counts and the development of obstructive lung disease: the Kangbuk Samsung Health Study

Hye Yun Park, Yoosoo Chang, Danbee Kang, Yun Soo Hong, Di Zhao, Jiin Ahn, Sun Hye Shin, Dave Singh, Eliseo Guallar, Juhee Cho, Seungho Ryu

Please cite this article as: Park HY, Chang Y, Kang D, *et al*. Blood eosinophil counts and the development of obstructive lung disease: the Kangbuk Samsung Health Study. *Eur Respir J* 2021; in press (https://doi.org/10.1183/13993003.03823-2020).

Blood eosinophil counts and the development of obstructive lung disease: the Kangbuk Samsung Health Study

Hye Yun Park[1*], Yoosoo Chang[2,3,4*], Danbee Kang[5], Yun Soo Hong[6], Di Zhao[6], Jiin Ahn[2], Sun Hye Shin[1], Dave Singh[7], Eliseo Guallar[4,6], Juhee Cho[2, 4, 5†], and Seungho Ryu[2,3,4†]

[1] Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea.

[2] Center for Cohort Studies, Total Healthcare Center, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea.

[3] Department of Occupational and Environmental Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea.

[4] Department of Clinical Research Design and Evaluation, SAIHST, Sungkyunkwan University, Seoul, South Korea.

[5] Center for Clinical Epidemiology, Samsung Medical Center, Seoul, South Korea.

[6] Department of Epidemiology and Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA.

[7] Medicines Evaluation Unit, University of Manchester, Manchester University NHS Foundation Trust, UK

[*] Drs. Hye Yun Park and Yoosoo Chang contributed equally as co-first authors.

[†] Drs. Seungho Ryu and Juhee Cho contributed equally as co-corresponding authors.

Address correspondence to:

Seungho Ryu, MD, PhD

Department of Occupational and Environmental Medicine
Kangbuk Samsung Hospital
Sungkyunkwan University School of Medicine
Samsung Main Building B2, 250, Taepyung-ro 2ga, Jung-gu, Seoul, Korea 04514
Telephone: +82-2-2001-5137, Fax: +82-2-757-0436
E-mail address: sh703.yoo@gmail.com

and

Juhee Cho, PhD
Department of Clinical Research Design and Evaluation
SAIHST
Sungkyunkwan University
81 Irwon-ro, Gangnam-gu, Seoul, 06351, Korea
E-mail: jcho@skku.edu

Funding: This paper was supported by SKKU Excellence in Research Award Research Fund, Sungkyunkwan University, 2020

Conflict of Interest Statement

Dr. Singh reports personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from Chiesi, personal fees from Cipla, personal fees from Genentech, personal fees from GlaxoSmithKline, personal fees from Glenmark, personal fees from Gossamerbio, personal fees from Menarini, personal fees from Mundipharma, personal fees from Novartis, personal fees from Peptinnovate, personal fees from Pfizer, personal fees from Pulmatrix, personal fees from Theravance, personal fees from Verona, outside the submitted work.

All other authors declare no competing interests.

Author Contributions

All authors contributed to and approved the final draft of the manuscript.

Conception and design: H.Y.P., Y.C., J.C., S.R.

Experiment and Data acquisition: Y.C., J.A., E.G., J.C., S.R.

Analysis and interpretation: H.Y.P., Y.C., D.K., Y.S.H., D.Z., J.A., D.S., E.G., J.C., S.R.

Drafting the manuscript: H.Y.P., Y.C., S.H.S., D.S., E.G., J.C., S.R.

Critical revision of the manuscript: H.Y.P., Y.C., D.K., Y.S.H., D.Z., J.A., S.H.S., D.S., E.G., J.C., S.R.

Acknowledgement

Dave Singh is supported by the National Institute for Health Research (NIHR) Manchester Biomedical Research Centre (BRC).

Running title: Blood eosinophil counts and COPD development

Take home message

Blood eosinophil counts were positively associated with the risk of developing of obstructive lung disease in large longitudinal cohort of young and middle-aged men and women.

Abstract word count: 203 words

Total word count (excluding title page, abstract, references, figure legend, and tables): 3,063 words

Abstract

The impact of blood eosinophil counts on the development of chronic obstructive lung disease (COPD) is unknown. We investigated whether a higher blood eosinophil counts was associated with the risk of developing obstructive lung disease (OLD) in a large cohort of men and women free lung disease at baseline.

Cohort study of 359,456 Korean adults without a history of asthma and without OLD at baseline who participated in health screening exams including spirometry. OLD was defined as pre-bronchodilator $FEV_1/FVC < 0.7$ and FEV_1 <80% predicted.

After a median follow-up of 5.6 years (interquartile range, 2.9–9.2), 5,008 participants developed incident OLD (incidence rate, 2.1 per 1,000 person-years; 95% CI, 2.1–2.2). In the fully-adjusted model, the HR (95% CI) for incident OLD comparing eosinophil counts of 100-<200, 200-<300, 300-<500 and ≥500 cells/μL to <100 cells/μL were 1.07 (1.00–1.15), 1.30 (1.20–1.42), 1.46 (1.33–1.60) and 1.72 (1.51–1.95) (P for trend <0.001). These associations were consistent in clinically relevant subgroups, including never, former, and current smokers.

In this large longitudinal cohort study, blood eosinophil counts were positively associated with the risk of developing of OLD. Our findings indicate a potential role of eosinophil count as an independent risk factor for developing COPD.

Keywords: Blood eosinophil counts; cohort study; lung function; obstructive lung disease; spirometry

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease associated with a substantial global burden of mortality, morbidity, and health care costs [1]. COPD is characterized by persistent respiratory symptoms and airflow limitation, but the symptoms and pathophysiological features show a marked variation from patient to patient despite a similar degree of airflow obstruction [2, 3]. There is substantial interest in identifying factors that could explain the high degree of variability observed in COPD patients.

Eosinophils are inflammatory cells that may be involved in the pathophysiology of COPD and may partially explain between-patient variability. Some COPD patients show increased numbers of eosinophils in lung tissue and sputum compared to healthy controls [4, 5], but the number of lung eosinophils varies considerably across COPD patients [5-7]. Airway eosinophilic inflammation is present in a subset of patients with COPD even when asthma or allergy are carefully excluded [8, 9], and higher tissue or blood eosinophil counts in COPD patients are associated with an increased gene expression of T helper type 2-high signature [10, 11]. In mouse models, lung eosinophilia was associated with elevated matrix metalloprotease -12 levels, a predictor of emphysema [12]. Furthermore, the number of eosinophils in lung tissue and blood are correlated in COPD patients [13-15], and higher blood eosinophil counts predicted a greater response to inhaled corticosteroids in several COPD randomized controlled trials [16-20]. Some studies have also reported that increased blood eosinophil counts were are associated with an increased frequency of exacerbations in COPD, although this association has been inconsistent [21-24].

Several cross-sectional and case-control studies have found an association between blood eosinophil counts and the presence of COPD or reduced lung function [25-30], but there is no available data on the association of blood eosinophil counts and the risk of

developing COPD during longitudinal follow up. Thus, we conducted a large longitudinal cohort study in men and women without COPD and without a history of asthma to investigate whether a higher blood eosinophil count was associated with the risk of developing obstructive lung disease (OLD) using pre-bronchodilator spirometry data.

Patients and Methods

Study population

The Kangbuk Samsung Health Study is a cohort study of adult men and women who underwent a comprehensive health examination at the clinics of the Total Healthcare Center of the Kangbuk Samsung Hospital in Seoul and Suwon, South Korea, since January 1, 2002 [31]. More than 80% of participants were employees of various companies or local governmental organizations, or their spouses. In Korea, annual or biennial health screening exams of employees are required by the Industrial Safety and Health Law and provided free of cost. The remaining participants voluntarily purchased health checkup exams at the center clinics.

The present cohort study included participants who underwent a comprehensive health examination between 2002 and 2017 and had at least one follow-up visit through December 31, 2019 (N = 411,903; **Figure 1**). We excluded participants with the following exclusion criteria at the baseline visit: missing data on body mass index, lung function, or blood eosinophil counts (n = 4,843); a self-reported history of physician diagnosed asthma or COPD or of surgery for lung or heart disease (n = 7,138); a history of malignancy including lung cancer (n = 5,639); abnormal lung function defined as either forced expiratory volume at 1 second (FEV_1)/forced vital capacity (FVC) < 0.7 (n=7,692), or FVC < 80% predicted (n=26,277); or blood white blood cells > 11,000 /mm^3 (n=3,487). Since some participants fulfilled more than one exclusion criteria, the final number of study participants was 359,456.

This study was approved by the institutional review board of Kangbuk Samsung Hospital (KBSMC 2020-06-055), which waived the requirement for written informed consent due to the use of de-identified data obtained as part of routine health screening examinations.

Data collection

At baseline and at each follow-up visit, data on demographic characteristics, medical history, medication use and lifestyle habits, including smoking status, were collected via standardized self-administered questionnaires. Smoking status was categorized into never, former, or current smoker. Alcohol intake was categorized into none, <20 g of ethanol/day, and ≥20 g of ethanol/day. The frequency of moderate or vigorous intensity physical activity was categorized into <3, and ≥3 times/week. Education level was categorized into less than college graduate and college graduate or more.

Anthropometric parameters and sitting blood pressure were measured by trained nurses. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Obesity was defined as BMI ≥25 kg/m^2, according to the proposed cutoff for obesity in Asians [32]. Hypertension was defined as a systolic blood pressure of ≥140 mmHg, a diastolic blood pressure of ≥90 mmHg, or current use of antihypertensive medication.

Each screening visit also included a spirometry test (without bronchodilator) performed according to the recommendations of the American Thoracic Society [33] using Vmax 22 spirometers (SensorMedics, Yorba Linda, CA, USA). Absolute values of FEV_1 and FVC were obtained, and the percentage of FEV_1 and FVC predicted values were calculated using a reference equation from a representative sample of Koreans [34]. OLD was defined as $FEV_1/FVC < 0.7$ and FEV_1 <80% predicted [35].

Blood samples were obtained after participants had fasted for at least 10 hours. Fasting blood measurements included glucose, lipid profile, insulin, high-sensitivity C-reative

protein (hsCRP), and glycated hemoglobin (HbA1c). Insulin resistance was assessed with the homeostatic model assessment for insulin resistance (HOMA-IR) equation as fasting blood insulin (uU/mL) × fasting blood glucose (mmol/L) / 22.5. Diabetes was defined as a fasting serum glucose ≥126 mg/dL, an HbA1c ≥6.5%, or current use of insulin or antidiabetic medications. White blood cell counts including differential counts were measured using an XE-2100 hematology analyzer (Sysmex Corporation, Kobe, Japan).[36] Absolute eosinophil counts were calculated by multiplying the total number of white blood cells by the percentage of eosinophils. Blood eosinophil counts were categorized into <100, 100-<200, 200-<300, 300-<500 and ≥500 cells/μL.

Statistical analyses

Intraclass correlation coefficient (ICC) and Kappa coefficient were used to assess the repeatability of blood eosinophil counts over time.

The primary endpoint was the development of OLD defined as FEV_1/FVC <0.7 and FEV_1 <80% predicted. Participants were followed up from the baseline examination until the visit of endpoint development or their last health examination, whichever occurred first. The incidence of OLD is evaluated at each visit and, therefore, the exact time of OLD development cannot be accurately identified and we can only determine that OLD occurred between the visits. To appropriately account for this type of censoring (interval censoring), we used a parametric proportional hazards model with natural cubic splines of log time with 3 internal knots at the 25^{th}, 50^{th}, and 75^{th} percentiles which allows for the estimation of smoothed baseline log cumulative hazards (Stata package stpm) [37]. We estimated the hazard ratios (HR) and 95% confidence intervals (CIs) for incident OLD comparing each category of blood eosinophil counts to the reference category of blood eosinophil counts <100 cells/μL. In addition to categorical analysis, we modeled blood eosinophil counts as

restricted cubic splines with knots at the 5th, 35th, 65th, and 95th percentiles of the sample distribution to provide a flexible estimate of the concentration-response relationship between blood eosinophil counts and incident OLD.

Models were first age- and sex-adjusted and then were further adjusted for other potential baseline confounders including study center (Seoul or Suwon), year of screening exam (1-year categories), smoking status (never, former, or current), alcohol intake (none, <20 g/day, ≥20 g/day, or unknown), BMI, history of pulmonary tuberculosis, hsCRP and blood neutrophil counts. In addition to using baseline eosinophil count as the primary exposure, we conducted additional analyses using blood eosinophil counts and potential confounders as time-varying covariates in the models. The proportional hazards assumption was assessed by examining graphs of estimated log(-log) survival curves. No violation of the proportional hazards assumption was found.

Because of the key role of smoking in the development of OLD, we performed subgroup analyses by smoking status. Additionally, we performed subgroup analyses by age (<40 vs. ≥40 years), sex (women vs. men), BMI (<25 vs. ≥25 kg/m^2), smoking (never, former, current), alcohol intake (<20 vs. ≥20 g/day), regular exercise (<3 vs. ≥3 time per week), and hsCRP (<1.0 vs. ≥1.0 mg/L). Interactions of blood eosinophil counts and participant characteristics, including smoking status, were tested using likelihood ratio tests that compared models with versus without interaction terms.

In sensitivity analysis, instead of using blood eosinophil counts, we used blood eosinophil percentage as exposure, categorized as <1, 1-<2, 2-<3, 3-<4, and ≥4%. In addition, we repeated the analysis after excluding participants with eosinophil count ≥600 cells/μL at baseline, after excluding participants with incident asthma over follow-up, and after including a self-reported physician-diagnosis of COPD in the questionnaire as part as the definition of incident OLD. All analyses were performed using Stata version 16 (StataCorp LP, College

Station, TX, USA). All p-values <0.05 were considered statistically significant.

Results

At baseline, the mean (SD) age of study participants was 36.7 (7.8) years, and 55.6% of participants were male (**Table 1**). The median blood eosinophil count at baseline was 127.7 cells/μL (interquartile range, 75.3–211.5). The frequency of participants with eosinophil counts <100, 100-<200, 200-<300, 300-<500 and ≥500 cells/μL at baseline were 38.0, 34.5, 14.8, 9.5, and 3.2%, respectively. The ICC of the eosinophil counts using repeated visits of study participants throughout follow-up was 0.53. The Kappa statistic for eosinophil count categories (<100, 100–299, and ≥300) comparing the 1st and 2nd visits in each participant was 0.44. The proportion of participants who remained in the same category of eosinophil count in the 1st and 2nd was 70.4% among those with <100 cells/μL in the 1st visit, 67.3% among those with 100–299 cells/μL and 51.9% among those with ≥300 cells/μL.

Participants with higher eosinophil counts were more likely to be male, current smokers, and alcohol drinkers, had a higher prevalence of obesity, hypertension, diabetes, and cardiovascular disease, had a less favorable lipid profile, and had higher average HOMA-IR, hs-CRP, and blood neutrophil counts.

After a median follow-up of 5.6 years (interquartile range, 2.9–9.2; maximum, 17.8 years; person-years, 2,349,412), 5,008 participants developed incident OLD (incidence rate, 2.1 per 1,000 person-years; 95% CI, 2.1–2.2). Among them, the proportion of never, former and current smokers were 36.0%, 26.7% and 37.4%, respectively. In the fully-adjusted model, the HR (95% CI) for incident OLD comparing eosinophil counts of 100-<200, 200-<300, 300-<500 and ≥500 cells/μL to <100 cells/μL were 1.07 (1.00–1.15), 1.30 (1.20–1.42), 1.46 (1.33–1.60) and 1.72 (1.51–1.95) (P for trend <0.001; **Table 2**). The adjusted HR for incident OLD associated with an increase of 100

cells/μL in eosinophil counts was 1.08 (95% CI 1.06–1.09). In spline regression models, the incidence of OLD increased throughout the range of eosinophil counts but the association was stronger at lower eosinophil counts (P value for nonlinear spline terms, < 0.001; **Figure 2**). The results were similar when blood eosinophil count and other confounders were treated as time-varying covariates (Table 2).

In sensitivity analyses, the findings were similar when we used eosinophil percentage instead of eosinophil count (**Supplementary Table S1**), when we excluded participants with incident asthma over follow up or with eosinophil count ≥600 cells/μL at baseline (**Supplementary Table S2**), or when we included a self-reported physician-diagnosis of COPD in the questionnaire as part as the definition of incident OLD (**Supplementary Table S3**).

In subgroup analyses stratified by smoking status, the concentration-response relationship between eosinophil count and risk of incident OLD was consistently observed among never, former, and current smokers (**Table 3** and **Figure 3**). The association of eosinophil count with the risk of OLD was also observed across clinically relevant subgroups, without significant interactions (**Supplementary Figure 1**).

Discussion

In this large cohort of 359,456 Korean adults with normal lung function and without COPD or asthma at baseline, blood eosinophil counts showed a progressive and independent association with the risk of developing incident OLD over follow-up. Participants with a blood eosinophil counts of ≥500 cells/μL had almost 2 times the risk of developing OLD compared to those with <100 cells/μL at baseline. This association was observed in never, former, and current smokers, and in all clinically relevant subgroups examined. These findings are consistent with the hypothesis that implicates blood eosinophils in the

pathophysiological process of OLD development [38].

Previous cross-sectional analyses using data from the Clinical Practice Research Datalink [26, 28] or general population data from Austria [25] reported that the blood eosinophil counts were significantly increased in COPD patients compared with control subjects. Another study showed that the blood eosinophil counts were significantly higher in COPD patients compared to smoker and to non-smoker controls (210, 140 and 120 cells/μL respectively), even after excluding asthma and atopy [27]. The novelty and strength of this study is the longitudinal analysis in a large cohort of relatively young subjects and the collection of detailed information which allowed us to investigate the association between blood eosinophil count and the development of incident OLD accounting for potential confounders.

Smoking is a major risk factor for COPD and is also associated with a higher eosinophil count [25]. Importantly, the prospective association between eosinophil count and COPD was evident in all groups of smokers, including never-smokers. Non-smoking COPD is increasingly recognized as a major subgroup of COPD cases [39, 40]. In our population, 36% of incident OLD cases originated in never smokers, including most cases of OLD in women. In addition to smoking, risk factors for COPD development include outdoor air pollution, exposure to biomass fuel, occupational exposure to dusts and gases, a history of tuberculosis, and poor socioeconomic status [40], but there is very limited data on the cellular and mediator profiles of airway inflammation in never-smoker COPD [41]. Our study suggests a potential role of eosinophils for COPD development in never smokers, which should be investigated further in mechanistic studies of never-smoker COPD pathogenesis.

In our study, the ICC of eosinophil counts over follow-up was 0.53 with moderate agreement for measurements obtained at different visits. Eosinophil counts can have high within-person variability, particularly for higher eosinophil counts, as inflammation is a

"dynamic" process and the level of inflammation is not constant in an individual [42, 43]. The results using eosinophil count at baseline, however, were similar to those using eosinophil counts as a time-varying variable, which accounts for changes in eosinophil counts over follow-up, suggesting that the association is driven by eosinophil counts over longer time periods.

Parasitic infection is one of the common causes of high eosinophil counts, but we did not collect information on the presence of parasitic infections. The distribution of blood eosinophil counts in our study population (median [interquartile range] 127.7 [75.3–211.5]), however, was similar to that from studies of other countries with lower prevalence of parasitic infection. For example, in Austria where the prevalence of parasitic infection was 0.24% between 1990–2000 [44], the median blood eosinophil count of 3,641 healthy individuals was 110 cells/μL (IQR:70–180) [25]. In another study from the United Kingdom, the median blood eosinophil counts of healthy smokers (n=46) and non-smokers (n=81) were 140 and 120 cells/μL, respectively [27]. In addition, most of our cohort participants were younger and had higher socioeconomic status than then general population in Korea, and the prevalence of parasitic infection in our study population is expected to be lower than in the general population.

The mechanisms underlying the association between blood eosinophil counts and COPD remain unclear. Noxious particles such as cigarette smoke can cause lung and systemic inflammation, including eosinophil activation; it is well known that cigarette smokers can develop acute eosinophilic pneumonia [45], while there is increasing recognition that inhalation of other products can also cause this [46, 47]. In support of this argument, we found that current smokers had higher eosinophil counts, a phenomenon that was also observed in an Austrian general population study [25]. In COPD patients, a high blood eosinophil count is associated with a higher number of lung eosinophils and with increased

levels of various inflammatory proteins in bronchoalveolar lavage and greater tissue remodeling [6, 7]. In our data, we observed a positive association between blood eosinophil counts and systemic inflammatory markers such as hsCRP and blood neutrophil counts, further implicating blood eosinophil counts as a biomarker connected to an increased inflammatory burden. However, the association between eosinophil counts and incident OLD persisted even after adjusting for hsCRP and blood neutrophil counts, suggesting that the role of eosinophils in COPD development depends on inflammatory mechanisms not fully captured by commonly used biomarkers. Future longitudinal research needs to establish the risk factors of eosinophilia and how eosinophil counts are associated with pathological changes in the lung in healthy (non-COPD) subjects.

The present study, however, has several limitations. First, our large longitudinal cohort used only spirometry testing without bronchodilator since post-bronchodilator spirometry was not routinely performed in health screening exams. We thus defined a $FEV_1/FVC < 0.7$ and $FEV_1 < 80\%$ predicted in pre-bronchodilator spirometry as OLD, not COPD [35]. However, since we excluded participants with a history of asthma, the presence of moderate-to-severe airflow limitation is likely to reflect COPD. Furthermore, our findings were virtually identical when we excluded participants who developed asthma over follow-up, and when our definition of incident OLD included a self-reported physician-diagnosis of COPD. Therefore, participants identified as having incident OLD using spirometric criteria in our study were likely to reflect those with incident COPD. Further studies using post-bronchodilator spirometry are necessary to corroborate the findings for COPD. Second, we did not measure some risk factors for COPD such as environmental or occupational exposures. Finally, the study population consisted of young and middle-aged Korean men and women who regularly attended health screening exams, which limits the generalizability of our findings to other populations. We note, however, that the distribution of eosinophil counts

in our study was similar to that of a general population study in Austria [25], and to that of a study of healthy non-COPD participants in the UK [27].

In conclusion, in this large cohort study, blood eosinophil counts were positively associated with the risk of developing OLD even among healthy individuals free of COPD or asthma and with normal lung function. The association between blood eosinophil counts and the risk of OLD was consistent in all subgroups examined, including never, former, and current smokers. Our findings suggest that individuals with higher eosinophil counts may benefit from closer monitoring of lung function in order to facilitate early detection and intervention of OLD.

References

1 Collaborators GBDCoD. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; 392: 1736-1788.

2 Agusti A, Calverley PM, Celli B, *et al*. Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respir Res* 2010; 11: 122.

3 Duffy S, Weir M, Criner GJ. The complex challenge of chronic obstructive pulmonary disease. *Lancet Respir Med* 2015; 3: 917-919.

4 Rutgers SR, Timens W, Kaufmann HF, *et al.* Comparison of induced sputum with bronchial wash, bronchoalveolar lavage and bronchial biopsies in COPD. *Eur Respir J* 2000; 15: 109-115.

5 Saha S, Brightling CE. Eosinophilic airway inflammation in COPD. *Int J Chron Obstruct Pulmon Dis* 2006; 1: 39-47.

6 Kolsum U, Damera G, Pham TH, *et al*. Pulmonary inflammation in patients with chronic obstructive pulmonary disease with higher blood eosinophil counts. *J Allergy Clin Immunol* 2017; 140: 1181-1184 e1187.

7 Eltboli O, Mistry V, Barker B, *et al*. Relationship between blood and bronchial submucosal eosinophilia and reticular basement membrane thickening in chronic obstructive pulmonary disease. *Respirology* 2015; 20: 667-670.

8 Brightling CE, Monteiro W, Ward R, *et al*. Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2000; 356: 1480-1485.

9 Kolsum U, Ravi A, Hitchen P, *et al*. Clinical characteristics of eosinophilic COPD versus COPD patients with a history of asthma. *Respir Res* 2017; 18: 73.

10 Christenson SA, Steiling K, van den Berge M, *et al.* Asthma-COPD Overlap. Clinical Relevance of Genomic Signatures of Type 2 Inflammation in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2015; 191: 758-766.

11 George L, Taylor AR, Esteve-Codina A, *et al.* Blood eosinophil count and airway epithelial transcriptome relationships in COPD versus asthma. *Allergy* 2020; 75: 370-380.

12 Doyle AD, Mukherjee M, LeSuer WE, *et al.* Eosinophil-derived IL-13 promotes emphysema. *Eur Respir J* 2019; 53.

13 Negewo NA, McDonald VM, Baines KJ, *et al.* Peripheral blood eosinophils: a surrogate marker for airway eosinophilia in stable COPD. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 1495-1504.

14 Singh D, Kolsum U, Brightling CE, *et al.* Eosinophilic inflammation in COPD: prevalence and clinical characteristics. *Eur Respir J* 2014; 44: 1697-1700.

15 Bafadhel M, McKenna S, Terry S, *et al.* Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med* 2011; 184: 662-671.

16 Siddiqui SH, Guasconi A, Vestbo J, *et al.* Blood Eosinophils: A Biomarker of Response to Extrafine Beclomethasone/Formoterol in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2015; 192: 523-525.

17 Bafadhel M, Peterson S, De Blas MA, *et al.* Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. *Lancet Respir Med* 2018; 6: 117-126.

18 Singh D, Bafadhel M, Brightling CE, *et al.* Blood Eosinophil Counts in Clinical Trials for Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2020.

19 Lipson DA, Barnhart F, Brealey N, *et al.* Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. *N Engl J Med* 2018; 378: 1671-1680.

20 Papi A, Vestbo J, Fabbri L, *et al.* Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet* 2018; 391: 1076-1084.

21 Bafadhel M, McKenna S, Terry S, *et al.* Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2012; 186: 48-55.

22 Vedel-Krogh S, Nielsen SF, Lange P, *et al.* Blood Eosinophils and Exacerbations in Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study. *Am J Respir Crit Care Med* 2016; 193: 965-974.

23 Couillard S, Larivee P, Courteau J, *et al.* Eosinophils in COPD Exacerbations Are Associated With Increased Readmissions. *Chest* 2017; 151: 366-373.

24 Mathioudakis AG, Bikov A, Foden P, *et al.* Change in blood eosinophils following treatment with inhaled corticosteroids may predict long-term clinical response in COPD. *Eur Respir J* 2020.

25 Hartl S, Breyer MK, Burghuber OC, *et al.* Blood eosinophil count in the general population: typical values and potential confounders. *Eur Respir J* 2020.

26 Landis S, Suruki R, Maskell J, *et al.* Demographic and Clinical Characteristics of COPD Patients at Different Blood Eosinophil Levels in the UK Clinical Practice Research Datalink. *COPD* 2018; 15: 177-184.

27 Kolsum U, Southworth T, Jackson N, *et al.* Blood eosinophil counts in COPD patients compared to controls. *Eur Respir J* 2019; 54.

28 Oshagbemi OA, Burden AM, Braeken DCW, *et al.* Stability of Blood Eosinophils in Patients with Chronic Obstructive Pulmonary Disease and in Control Subjects, and the Impact of Sex, Age, Smoking, and Baseline Counts. *Am J Respir Crit Care Med* 2017; 195: 1402-1404.

29 Hancox RJ, Pavord ID, Sears MR. Associations between blood eosinophils and decline in lung function among adults with and without asthma. *Eur Respir J* 2018; 51.

30 Mogensen I, Vonk JM, Wijnant SRA, *et al.* Blood eosinophil level and lung function trajectories: cross-sectional and longitudinal studies in European cohorts. *ERJ Open Res* 2020; 6.

31 Chang Y, Ryu S, Choi Y, *et al.* Metabolically Healthy Obesity and Development of Chronic Kidney Disease: A Cohort Study. *Ann Intern Med* 2016; 164: 305-312.

32 World Health Organization, Regional Office for the Western Pacific. The Asia-Pacific perspective: redefining obesity and its treatment. Sydney, Health Communications Australia, 2000.

33 Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005; 26: 319-338.

34 Choi HS, Park YB, Yoon HK, *et al.* Validation of Previous Spirometric Reference Equations and New Equations. *J Korean Med Sci* 2019; 34: e304.

35 Lange P, Celli B, Agusti A, *et al.* Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2015; 373: 111-122.

36 Ruzicka K, Veitl M, Thalhammer-Scherrer R, *et al.* The new hematology analyzer Sysmex XE-2100: performance evaluation of a novel white blood cell differential technology. *Arch Pathol Lab Med* 2001; 125: 391-396.

37 Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat Med* 2002; 21: 2175-2197.

38 Bafadhel M, Pavord ID, Russell REK. Eosinophils in COPD: just another biomarker? *Lancet Respir Med* 2017; 5: 747-759.

39 Zhou Y, Wang C, Yao W, *et al.* COPD in Chinese nonsmokers. *Eur Respir J* 2009; 33: 509-

518.

40 Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. *Lancet* 2009; 374: 733-743.

41 Salvi SS, Brashier BB, Londhe J, *et al.* Phenotypic comparison between smoking and non-smoking chronic obstructive pulmonary disease. *Respir Res* 2020; 21: 50.

42 Higham A, Leow-Dyke S, Jackson N, *et al.* Stability of eosinophilic inflammation in COPD bronchial biopsies. *Eur Respir J* 2020; 56.

43 Long GH, Southworth T, Kolsum U, *et al.* The stability of blood Eosinophils in chronic obstructive pulmonary disease. *Respir Res* 2020; 21: 15.

44 Tomaso H, Dierich MP, Allerberger F. Helminthic infestations in the Tyrol, Austria. *Clin Microbiol Infect* 2001; 7: 639-641.

45 Sousa C, Rodrigues M, Carvalho A, *et al.* Diffuse smoking-related lung diseases: insights from a radiologic-pathologic correlation. *Insights Imaging* 2019; 10: 73.

46 Chaaban T. Acute eosinophilic pneumonia associated with non-cigarette smoking products: a systematic review. *Adv Respir Med* 2020; 88: 142-146.

47 Gulsen A, Uslu B. Health Hazards and Complications Associated with Electronic Cigarettes: A Review. *Turk Thorac J* 2020; 21: 201-208.

Figure legends

Figure 1. Flow chart of study participants.

Figure 2. Multivariable-adjusted hazard ratios (95% CI) for incident OLD by blood eosinophil counts.

The curves represent adjusted hazard ratios (solid line) and their 95% confidence intervals (dashed lines) for incident OLD based on restricted cubic splines for blood eosinophil counts with knots at the 5^{th}, 35^{th}, 65^{th}, and 95^{th} percentiles (blood eosinophil counts 32.7, 92.7, 169.9, and 429.1 cells/μL, respectively) of their sample distribution. The reference value (diamond dot) was set at the 10^{th} percentile (blood eosinophil count 48.1 cells/μL). The model was adjusted for age, sex, center, year of screening exam, BMI, smoking status, alcohol intake, history of pulmonary tuberculosis, hsCRP, and blood neutrophil counts.

Abbreviations: BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; OLD, obstructive lung disease.

Figure 3: Multivariable-adjusted hazard ratios for incident OLD by blood eosinophil counts for never, former, and current smokers.

The curves represent adjusted hazard ratios for incident OLD based on restricted cubic splines for blood eosinophil counts with knots at the 5^{th}, 35^{th}, 65^{th}, and 95^{th} percentiles of their sample distribution. The reference value (diamond dot) was set at the 10^{th} percentile. Estimates were adjusted by age, sex, center, year of screening exam, BMI, alcohol intake, history of pulmonary tuberculosis, hsCRP, and blood neutrophil counts.

Abbreviations: BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; OLD, obstructive lung disease.

Supplement Figure 1

Multivariable-adjusted hazard ratios (95% CI) for incident OLD comparing ≥ 500 cells/μL to < 100 cells/μL of eosinophil count category in pre-specified subgroups.

Models were adjusted for age, sex, center, year of screening exam, BMI, smoking status, alcohol intake, history of pulmonary tuberculosis, hsCRP, and blood neutrophil counts.

Abbreviations: BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; OLD, obstructive lung disease.

Table 1. Baseline characteristics of study participants.

Characteristics	Overall	Eosinophil count category (cells/μL)				
		<100	100-199	200-299	300-499	≥ 500
Number	359,456	136,587	124,034	53,256	34,238	11,341
Age (years)[a]	36.7 (7.8)	36.5 (7.9)	36.7 (7.8)	36.9 (7.7)	37.1 (7.6)	37.8 (7.9)
Male (%)	55.6	43.0	57.7	67.7	72.5	76.3
BMI (kg/m^2)	23.3 (3.3)	22.6 (3.1)	23.5 (3.3)	23.9 (3.3)	24.0 (3.3)	24.2 (3.2)
Obesity (%)[f]	28.0	20.9	29.7	34.9	35.6	38.3
Current smoker (%)	23.0	13.1	23.5	32.7	38.7	44.0
Alcohol intake (%) [c]	18.3	14.1	18.4	22.5	24.3	29.3
Regular exercise (%) [d]	14.2	14.3	14.2	14.1	13.9	14.3
High education level (%) [e]	81.0	79.6	81.6	82.4	82.6	79.7
Comorbidities						
Diabetes (%)	2.3	1.8	2.4	2.9	3.0	3.5
Hypertension (%)	10.9	8.9	11.2	12.8	13.6	15.0
History of pulmonary TB (%)	2.9	2.8	3.0	3.0	3.0	3.1
History of CVD (%)	2.1	1.9	2.1	2.1	2.4	2.7
Laboratory findings						
FBG (mg/dl) [a]	93.6 (13.7)	92.6 (12.8)	93.8 (13.8)	94.5 (14.5)	94.8 (14.9)	95.3 (15.0)
Total cholesterol (mg/dL)[a]	192.4 (34.1)	189.4 (33.6)	193.2 (34.2)	194.9 (34.3)	196.1 (34.0)	197.4 (34.6)
LDL-C (mg/dl) [a]	115.5 (30.9)	112.7 (30.5)	116.3 (31.0)	118.0 (31.0)	119.0 (30.7)	119.2 (31.7)
HDL-C (mg/dl) [a]	57.8 (14.4)	60.3 (14.8)	57.2 (14.2)	55.6 (13.7)	54.9 (13.4)	54.2 (13.0)
Triglycerides (mg/dL)[b]	93 (65-138)	81 (59-117)	96 (68-142)	105 (73-157)	110 (77-163)	118 (80-175)
ALT (U/L)[b]	19 (13-29)	17 (12-25)	19 (14-29)	21 (15-32)	22 (15-33)	23 (16-34)
hsCRP (mg/L)[b]	0.3 (0.1-0.4)	0.3 (0.1-0.4)	0.3 (0.1-0.4)	0.3 (0.2-0.4)	0.3 (0.2-0.4)	0.3 (0.3-0.5)
HOMA-IR [b]	1.21 (0.81-1.79)	1.13 (0.75-1.66)	1.25 (0.83-1.85)	1.29 (0.86-1.92)	1.30 (0.86-1.93)	1.30 (0.86-1.98)
Neutrophil count	3110.0 (2503.8-3871.6)	2962.4 (2370.0-3726.0)	3124.6 (2535.8-3864.1)	3240.9 (2624.9-3996.0)	3320.5 (2692.2-4096.3)	3442.5 (2805.8-4218.5)
Pulmonary function test						
FEV_1 (L)	3.41 (0.62)	3.28 (0.62)	3.44 (0.62)	3.55 (0.59)	3.59 (0.57)	3.62 (0.56)
FEV_1 (% pred)	101.9 (13.9)	102.0 (13.7)	101.9 (14.1)	101.7 (14.1)	101.5 (14.1)	101.6 (14.5)
FVC (L)	4.11 (0.81)	3.92 (0.80)	4.14 (0.81)	4.29 (0.77)	4.35 (0.74)	4.40 (0.72)
FVC (% pred)	99.3 (12.3)	99.4 (12.3)	99.3 (12.4)	99.1 (12.3)	98.9 (12.1)	99.0 (12.2)
FEV_1/FVC	85.7 (6.5)	86.2 (6.5)	85.6 (6.4)	85.2 (6.5)	85.0 (6.5)	84.7 (6.6)

Number of visits [b]	7 (4-10)	6 (4-10)	7 (4-10)	7 (4-11)	7 (4-11)	7 (4-11)
Interval between each visit (years) [b]	1.2 (1.0-2.0)	1.2 (1.0-2.0)	1.2 (1.0-2.0)	1.2 (1.0-2.0)	1.1 (1.0-2.0)	1.1 (1.0-2.0)

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; CVD, cardiovascular disease; FBG, fasting blood glucose; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; TB, tuberculosis.

Values in Table are [a]mean (standard deviation), [b]median (interquartile range), or percentage.

[c] ≥ 20 g/day; [d] ≥ 3 times/week; [e] ≥ College graduate; [f] BMI ≥ 25kg/m^2.

Table 2. Hazard ratios (95% confidence intervals) for the development of OLD by eosinophil count categories.

	Eosinophil count category (cells/μL)					Per 100 (cells/μL) increase in eosinophil counts
	<100	100-199	200-299	300-499	≥ 500	
Person-years (PY)	856,106.9	821,839.7	359,837.4	233,849.3	77,778.2	
Incident cases	1,428	1,623	936	714	307	
ID (cases per 10^3 PY)	1.7	2.0	2.6	3.1	3.9	
Multivariable-adjusted HR (95% CI)[b]						
Model 1	*Reference*	1.11 (1.03-1.19)	1.39 (1.28-1.51)	1.59 (1.45-1.75)	1.95 (1.72-2.21)	1.09 (1.08-1.11)
Model 2	*Reference*	1.07 (1.00-1.15)	1.30 (1.20-1.42)	1.46 (1.33-1.60)	1.72 (1.51-1.95)	1.08 (1.06-1.09)
HR (95% CI)[c] in time-varying model	*Reference*	1.11 (1.04-1.20)	1.36 (1.25-1.48)	1.43 (1.30-1.57)	1.85 (1.62-2.10)	1.06 (1.05-1.07)

[a] Values are median (range).

[b] Estimated from parametric proportional hazards models. Model 1: adjusted for age and sex. Model 2: Model 1 plus adjustment for center, year of screening exam, BMI, smoking status, alcohol intake, history of pulmonary tuberculosis, hsCRP, and blood neutrophil counts.

[c] Estimated from parametric proportional hazard models with baseline age, sex, center, and year of screening exam as time-fixed variables and blood eosinophil count categories, BMI, smoking status, alcohol intake, history of pulmonary tuberculosis, hsCRP and neutrophil counts as time-varying variables.

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; hsCRP, high sensitivity C-reactive protein: ID, incidence density; OLD, obstructive lung disease.

Table 3. Hazard ratios (95% confidence intervals) for the development of OLD by eosinophil count and smoking status categories.

Subgroup	Eosinophil count category (cells/μL)				
	<100	100-199	200-299	300-499	≥500
Never smokers					
Total Number	86,263	62,683	21,939	12,244	3,526
Incident cases	709	556	228	159	66
HR (95% CI)	*Reference*	1.04 (0.93-1.16)	1.19 (1.03-1.39)	1.47 (1.24-1.75)	1.93 (1.50-2.49)
Former smokers					
Total Number	26,215	27,549	12,295	7,803	2,565
Incident cases	349	473	224	159	69
HR (95% CI)	*Reference*	1.23 (1.07-1.41)	1.26 (1.06-1.50)	1.40 (1.16-1.69)	1.80 (1.39-2.33)
Current smokers					
Total Number	16,996	27,741	16,598	12,651	4,793
Incident cases	278	530	447	373	159
HR (95% CI)	*Reference*	1.06 (0.92-1.23)	1.47 (1.26-1.71)	1.57 (1.35-1.84)	1.65 (1.36-2.01)

[a] Estimated from parametric proportional hazards models adjusted for age, sex, center, year of screening exam, BMI, alcohol intake, history of pulmonary tuberculosis, hsCRP and blood neutrophil counts.
The number of incident OLD patients with missing information on smoking status was 229 (4.6%).
Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; OLD, obstructive lung disease.

Supplementary appendix
Table S1. Hazard ratios (95% confidence intervals) for the development of OLD by eosinophil % categories.

	Eosinophil % category				
	<1.0	1.0-1.9	2.0-2.9	3.0-3.9	≥4.0
Person-years (PY)	273,391.6	702,031.5	533,311.3	327,889.7	512,787.6

Incident cases	408	1,273	1,083	780	1,464
ID (cases per 10^3 PY)	1.5	1.8	2.0	2.4	2.9
Multivariable-adjusted HR (95% CI) [a]					
Model 1	*Reference*	1.15 (1.03-1.29)	1.25 (1.11-1.40)	1.41 (1.25-1.59)	1.63 (1.46-1.82)
Model 2	*Reference*	1.13 (1.01-1.27)	1.21 (1.08-1.36)	1.35 (1.20-1.53)	1.55 (1.38-1.74)
HR (95% CI)[b] in time-varying model	*Reference*	1.00 (0.90-1.11)	1.07 (0.96-1.20)	1.21 (1.08-1.36)	1.35 (1.21-1.51)

[a] Estimated from parametric proportional hazards models. Model 1: adjusted for age and sex. Model 2: Model 1 plus adjustment for center, year of screening exam, BMI, smoking status, alcohol intake, history of pulmonary tuberculosis, hsCRP and blood neutrophils (percentage).

[b] Estimated from parametric proportional hazard models with baseline age, sex, center, and year of screening exam as time-fixed variables and blood eosinophil % categories, smoking status, alcohol intake, BMI, history of tuberculosis, hsCRP and blood neutrophil percentage as time-varying variables.

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; hsCRP, high sensitivity C-reactive protein: ID, incidence density; OLD, obstructive lung disease.

Table S2. Multivariable-adjusted hazard ratios (95% confidence intervals) for the development of OLD by eosinophil count categories after applying additional exclusion criteria.

	Eosinophil count category (cells/μL)				
	<100	100-199	200-299	300-499	≥ 500
After excluding participants with incident asthma over follow-up (a)	*Reference*	1.06 (0.98-1.14)	1.25 (1.15-1.37)	1.31 (1.19-1.45)	1.55 (1.36-1.78)
After excluding participants with eosinophil count ≥600 at baseline (b)	*Reference*	1.07 (1.00-1.15)	1.31 (1.20-1.43)	1.47 (1.34-1.61)	1.65 (1.37-1.99)
(a) + (b)	*Reference*	1.06 (0.98-1.14)	1.25 (1.15-1.37)	1.31 (1.19-1.45)	1.50 (1.23-1.83)

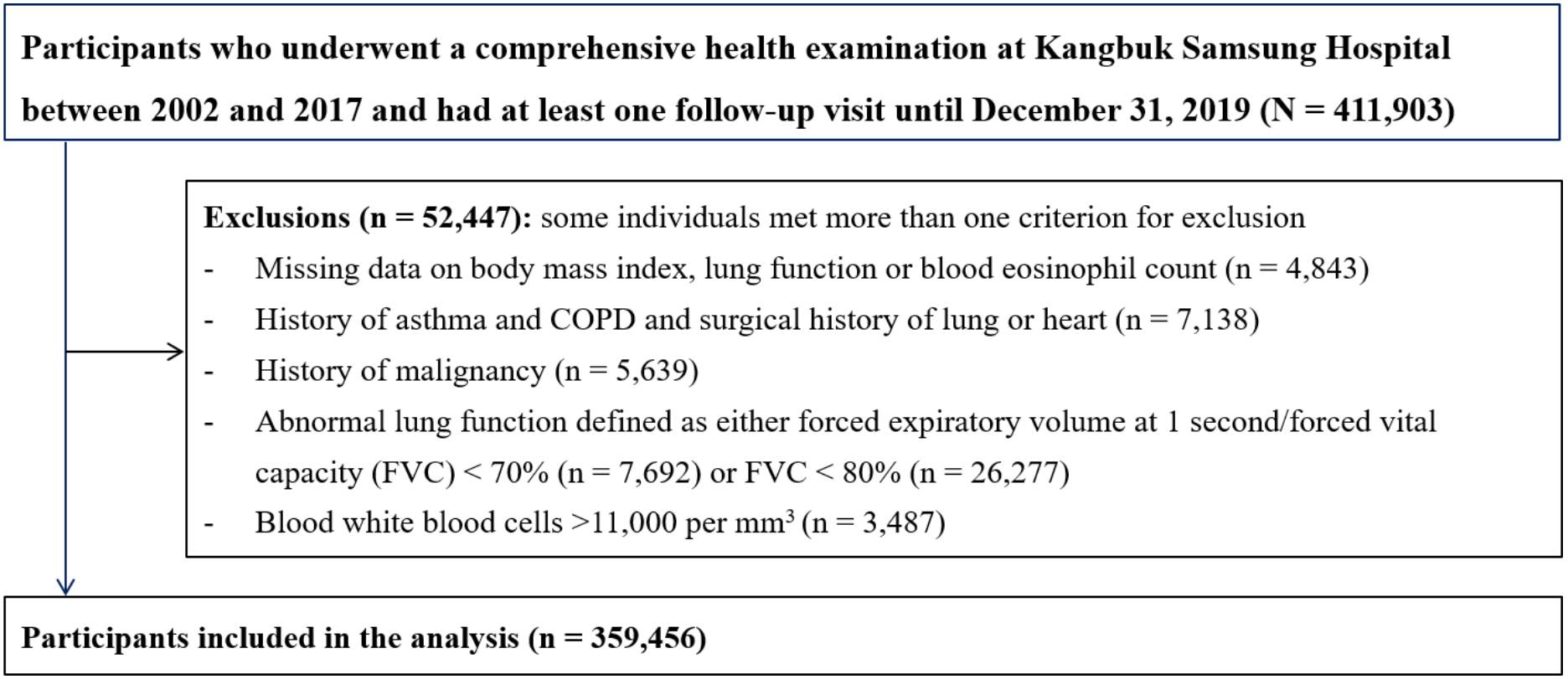
Hazard ratios and 95% confidence intervals estimated from parametric proportional hazard models adjusted for age, sex, center, year of screening exam, BMI, smoking, alcohol intake, history of pulmonary tuberculosis, hsCRP and blood neutrophil counts.
Abbreviations: BMI, body mass index; hsCRP, high sensitivity C-reactive protein; OLD, obstructive lung disease.

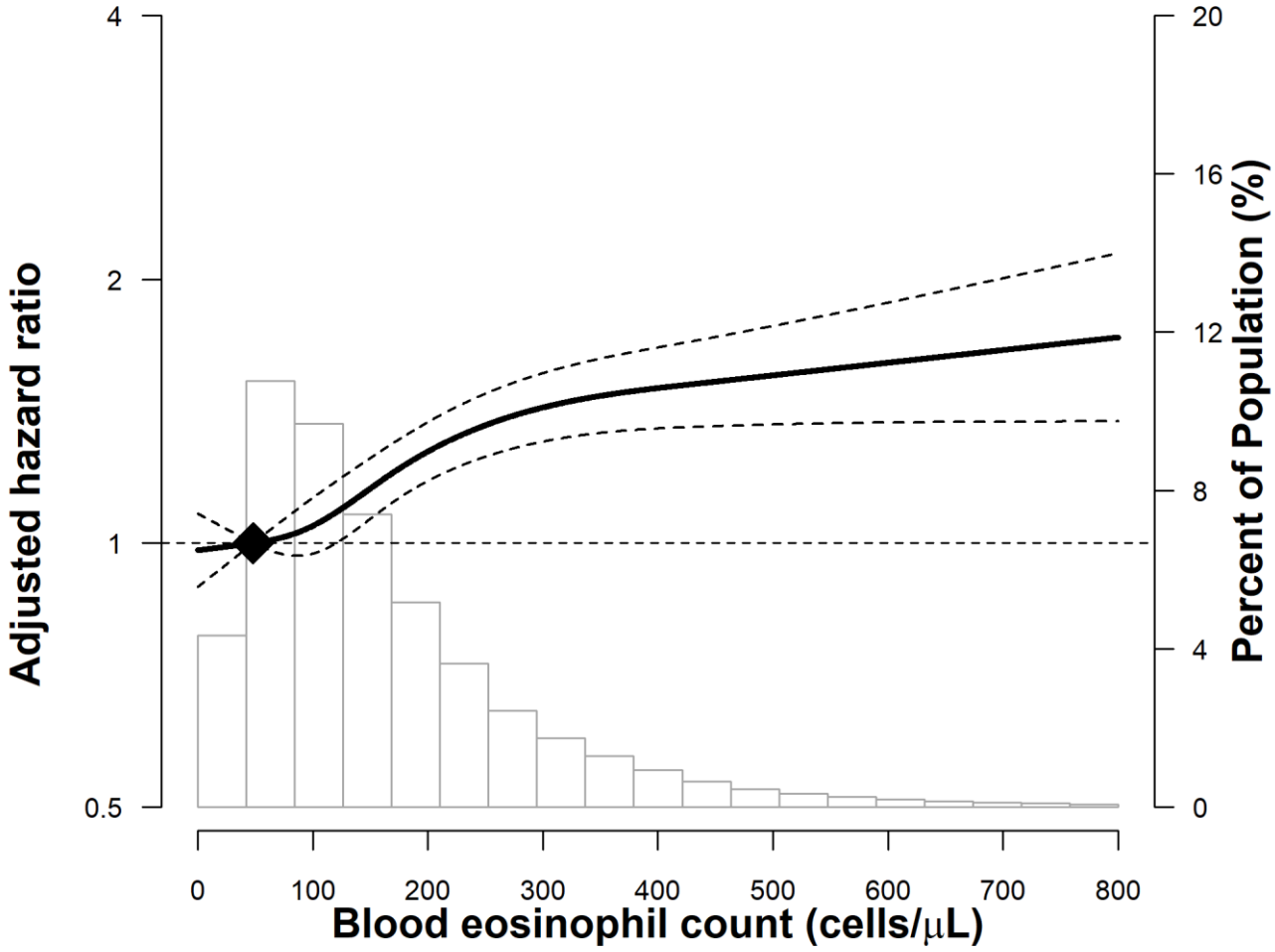
Table S3. Multivariable-adjusted hazard ratios (95% confidence intervals) for the development of OLD by eosinophil count categories according to different criteria to identify incident OLD (lung function test, self-reported of a physician-diagnosis, or both)

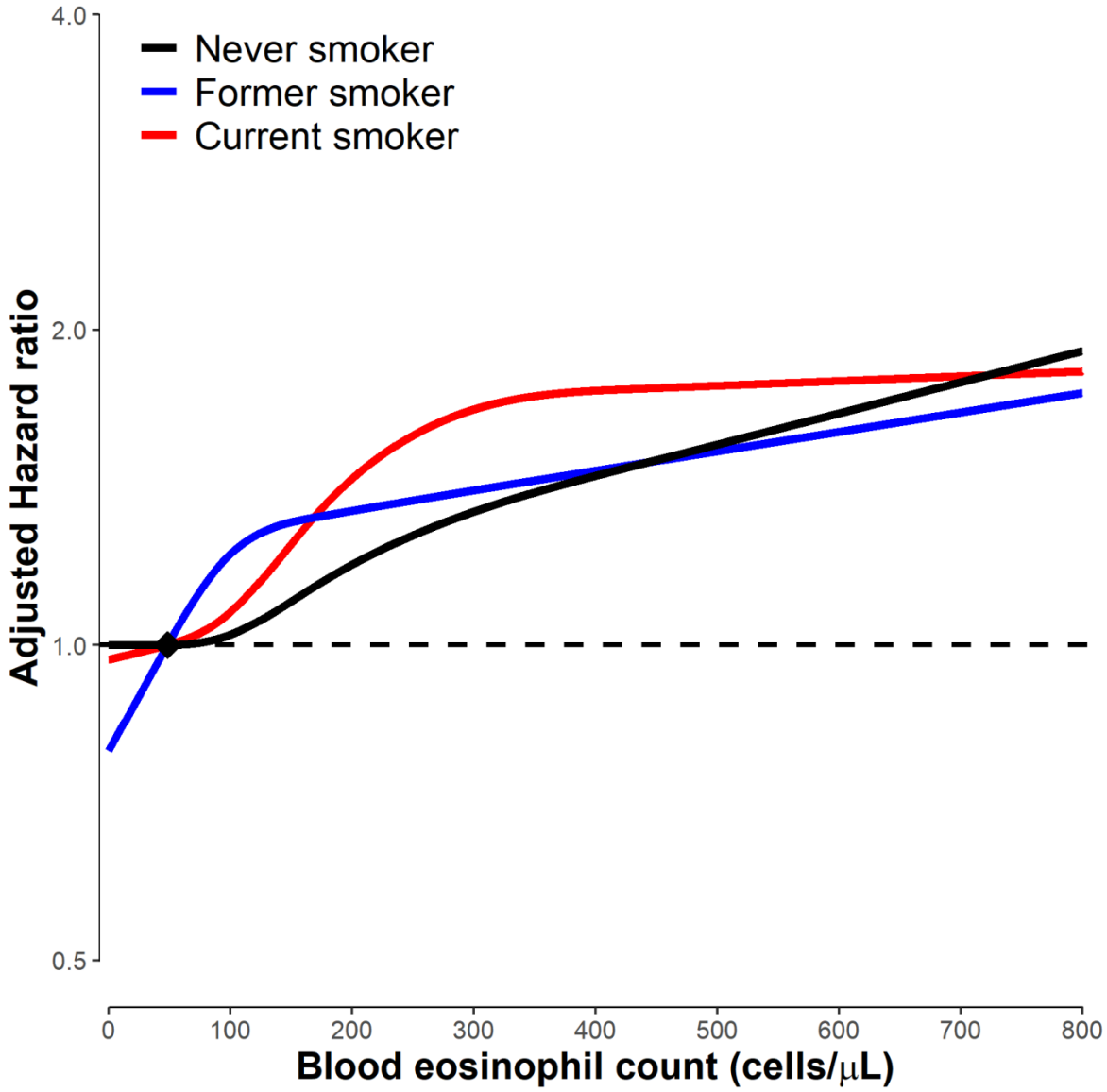
	Eosinophil count category (cells/μL)				
	<100	100-199	200-299	300-499	≥ 500
Lung function test (pre-bronchodilator $FEV_1/FVC < 70\%$ & $FEV_1 < 80\%$ pred (a)	*Reference*	1.07 (1.00-1.15)	1.30 (1.20-1.42)	1.46 (1.33-1.60)	1.72 (1.51-1.95)
Self-reported of a physician-diagnosis of COPD (b)	*Reference*	1.13 (1.05-1.21)	1.11 (1.02-1.21)	1.25 (1.14-1.37)	1.30 (1.14-1.49)
(a) + (b)	*Reference*	1.11 (1.05-1.16)	1.20 (1.13-1.27)	1.33 (1.24-1.42)	1.49 (1.36-1.64)

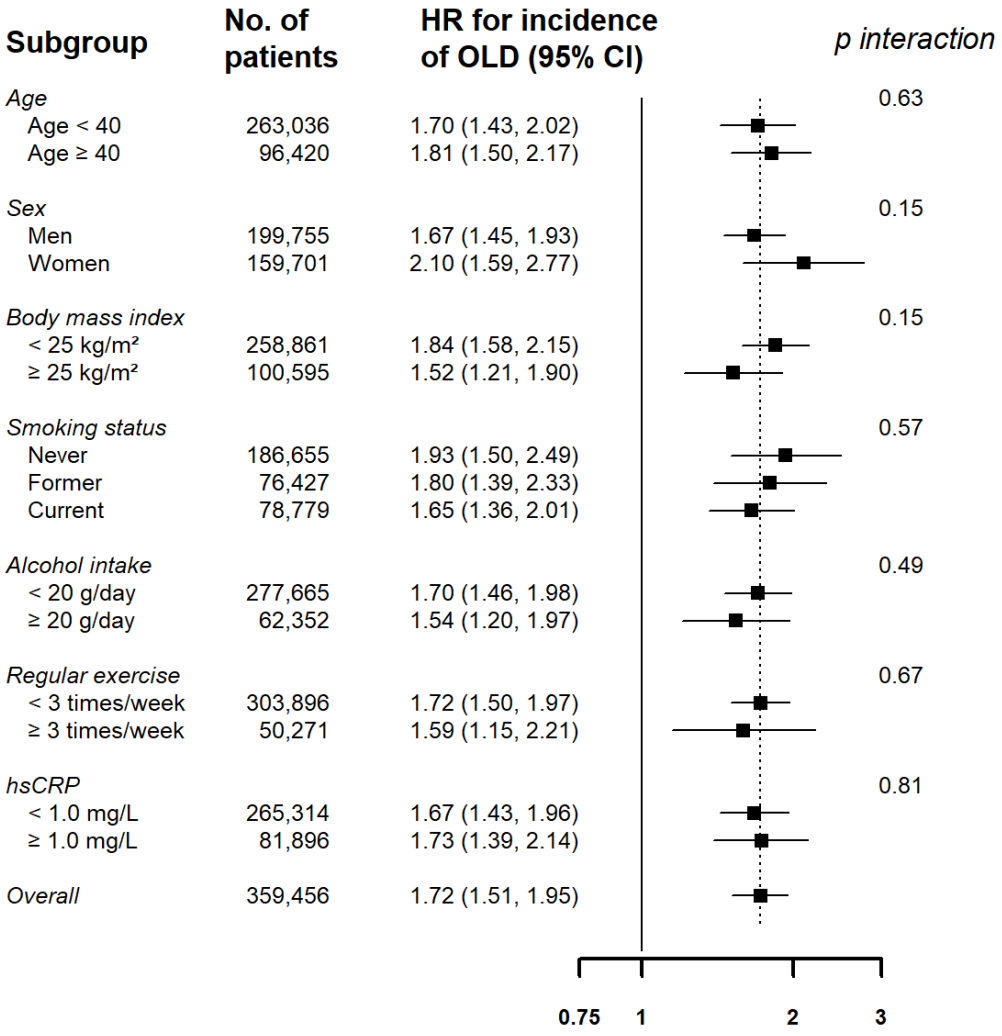
Hazard ratios and 95% confidence intervals estimated from parametric proportional hazard models adjusted for age, sex, center, year of screening exam, BMI, smoking, alcohol intake, history of pulmonary tuberculosis, hsCRP and blood neutrophil counts.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; hsCRP, high sensitivity C-reactive protein; OLD, obstructive lung disease.


Participants who underwent a comprehensive health examination at Kangbuk Samsung Hospital between 2002 and 2017 and had at least one follow-up visit until December 31, 2019 (N = 411,903)
Exclusions (n = 52,447): some individuals met more than one criterion for exclusion
- Missing data on body mass index, lung function or blood eosinophil count (n = 4,843)
- History of asthma and COPD and surgical history of lung or heart (n = 7,138)
- History of malignancy (n = 5,639)
- Abnormal lung function defined as either forced expiratory volume at 1 second/forced vital capacity (FVC) < 70% (n = 7,692) or FVC < 80% (n = 26,277)
- Blood white blood cells >11,000 per mm3 (n = 3,487)
Participants included in the analysis (n = 359,456)


Adjusted hazard ratio
4
2
1
0.5
Percent of Population (%)
20
16
12
8
4
0
0
100
200
300
400
500
600
700
800
Blood eosinophil count (cells/μL)


Never smoker
Former smoker
Current smoker
Adjusted Hazard ratio
4.0
2.0
1.0
0.5
0
100
200
300
400
500
600
700
800
Blood eosinophil count (cells/μL)


Subgroup
No. of patients
HR for incidence of OLD (95% CI)
p interaction
Age
Age < 40 263,036 1.70 (1.43, 2.02)
Age ≥ 40 96,420 1.81 (1.50, 2.17)
0.63
Sex
Men 199,755 1.67 (1.45, 1.93)
Women 159,701 2.10 (1.59, 2.77)
0.15
Body mass index
< 25 kg/m² 258,861 1.84 (1.58, 2.15)
≥ 25 kg/m² 100,595 1.52 (1.21, 1.90)
0.15
Smoking status
Never 186,655 1.93 (1.50, 2.49)
Former 76,427 1.80 (1.39, 2.33)
Current 78,779 1.65 (1.36, 2.01)
0.57
Alcohol intake
< 20 g/day 277,665 1.70 (1.46, 1.98)
≥ 20 g/day 62,352 1.54 (1.20, 1.97)
0.49
Regular exercise
< 3 times/week 303,896 1.72 (1.50, 1.97)
≥ 3 times/week 50,271 1.59 (1.15, 2.21)
0.67
hsCRP
< 1.0 mg/L 265,314 1.67 (1.43, 1.96)
≥ 1.0 mg/L 81,896 1.73 (1.39, 2.14)
0.81
Overall 359,456 1.72 (1.51, 1.95)
0.75
1
2
3