Rethinking blood eosinophil counts: Epidemiology, associated chronic diseases, and increased risks of cardiovascular disease

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Background: The distribution and determinants of blood eosinophil counts in the general population are unclear. Furthermore, whether elevated blood eosinophil counts increase risk for cardiovascular disease (CVD) and other chronic diseases, other than atopic conditions, remains uncertain. Objective: We sought to describe the distribution of eosinophil counts in the general population and determine the association of eosinophil count with prevalent chronic disease and incident CVD. Methods: A population-based adult cohort was followed from January 1, 2006, to December 31, 2020. Electronic health record data regarding demographic characteristics, prevalent clinical characteristics, and incident CVD were extracted. Associations between blood eosinophil counts and demographic characteristics, chronic diseases, laboratory values, and risks of incident CVD were assessed using chi-square test, ANOVA, and Cox proportional hazards regression.

Results: Blood eosinophil counts increased with age, body mass index, and reported smoking and tobacco use. The prevalence of chronic obstructive pulmonary disease, hypertension, cardiac arrhythmias, hyperlipidemia, diabetes mellitus, chronic kidney disease, and cancer increased as eosinophil counts increased. Eosinophil counts were significantly associated with coronary heart disease (hazard ratio [HR], 1.44; 95% CI, 1.12-1.84) and heart failure (HR, 1.62; 95% CI, 1.30-2.01) in fully adjusted models and with stroke/transient ischemic attack (HR, 1.37; 95% CI, 1.16-1.61) and CVD death (HR, 1.49; 95% CI, 1.10-2.00) in a model adjusting for age, sex, race, and ethnicity. Conclusions: Blood eosinophil counts differ by demographic and clinical characteristics as well as by prevalent chronic disease. Moreover, elevated eosinophil counts are associated with risk of CVD. Further prospective investigations are needed to determine the utility of eosinophil counts as a biomarker for CVD risk. (J Allergy Clin Immunol Global 2022;1:233-40.)

Key words: Eosinophil, count, epidemiology, cardiovascular disease, risk

Eosinophils are bone-marrow–derived multifaceted leukocytes involved in tissue homeostasis, immune regulation, and inflammation. Since eosinophils were first described in 1879, their clinical importance has been widely attributed to host defense to helminths and other parasites as well as to their pathologic role in allergic diseases and asthma. This rather limited view of eosinophils has been reexamined as evidence has emerged that eosinophils may have a much larger role in human health and disease. Eosinophils are now thought to have a pathophysiologic role in several chronic diseases including cardiovascular disease (CVD), cancer, diabetes, and chronic kidney disease, although the precise mechanisms by which eosinophils impact chronic diseases, other than atopic conditions, is not well defined.

Blood eosinophil counts may serve as a prognostic and/or susceptibility biomarker for various chronic diseases, because they are already recommended to be used for the management of asthma and chronic obstructive pulmonary disease (COPD) in recent guidelines. Whether elevated eosinophil counts are a risk factor for chronic diseases, other than asthma or COPD, remains uncertain. Much of this uncertainty stems from lack of knowledge regarding the distribution and determinants of eosinophil counts in the general population. Studies focusing on the distribution and determinants of eosinophil counts in the general population are lacking, and the natural history of eosinophilia is undetermined.

Associations between eosinophils and CVD have been of particular interest, because morbidity and mortality due to cardiac complications have been well described in conditions with prolonged eosinophilia and hypereosinophilia, such as in hypereosinophilic syndrome and eosinophilic granulomatosis with polyangiitis. Cardiac complications occur in 20% to 50% of these patients and include myocarditis, which can cause heart failure and sudden death, cardiomyopathy, and thromboembolic

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In the broader context of those not having eosinophilia to the level seen in hypereosinophilic syndrome or eosinophilic granulomatosis with polyangiitis, previous studies have reported increased risk of coronary heart disease (CHD) with elevated eosinophil counts, eosinophil cationic protein as a biomarker for CHD severity, eosinophil counts being positively correlated with coronary artery calcification, and higher eosinophil counts being associated with increased long-term mortality after percutaneous coronary intervention. However, these previous studies all involved individuals with either known CHD demonstrated by angiography or were highly suspicious to have CHD due to a history of stable angina, unstable angina, or myocardial infarction. Few studies have addressed eosinophil counts for individuals in the general population initially free of CVD for risks for the development of new cases of CVD (incident CVD).

Our study addresses these knowledge gaps regarding eosinophil counts by using comprehensive electronic health record data over a 15-year period to describe the distribution of eosinophil counts in the population by demographic and clinical characteristics. In addition, we determine the association of eosinophil counts with prevalent chronic diseases. Finally, we characterize the risks of eosinophil counts with incident CVD.

**METHODS**

**Setting**

This study uses the resources of the Rochester Epidemiology Project (REP). In brief, the REP is a population-based medical records–linkage system that unifies records from multiple medical care providers located in a 27-county region in southern Minnesota and western Wisconsin. The REP includes the 2 largest providers of care in the region, namely Mayo Clinic, Mayo Clinic Health System clinics and hospitals, and Olmsted Medical Center and its affiliated clinics. Each health care provider in these counties uses a unit (or dossier) medical record system whereby all data collected on a person are assembled in one place. The REP captures and classifies information from these records including demographic data, diagnostic and procedure codes, laboratory test results, prescriptions, hospitalizations, emergency room visits, nursing home care, vitals data, tobacco use, and death data.

By capturing and updating comprehensive phenotypic health care data through this medical records–linkage system, the REP is uniquely positioned to characterize longitudinal disease trajectories and outcomes.

**Participants**

We leveraged an existing REP cohort of all individuals aged 30 years or older who resided in Olmsted County, Minn, on January 1, 2006. The age cutoff of 30 years was chosen because CVD is infrequent in the pediatric population and adults aged 18 to 29 years. In addition, traditional CVD risk factors are not routinely assessed in the younger population. The index date of January 1, 2006, allows for a multiyear follow-up to evaluate incident events. All included individuals provided consent through Minnesota research authorization. This study was approved by the Mayo Clinic and Olmsted Medical Center institutional review boards.

**Measurements**

Data extraction, harmonization, and processing have been previously described. In brief, demographic variables, CVD risk factors, and comorbidities were extracted from the REP. All baseline variables were extracted from January 1, 2001, to December 31, 2005. Heights and weights were retained, and all possible body mass index (BMI) combinations were calculated (weight (kg)/height (m²)). The median BMI was calculated and considered the baseline BMI. The most recent recorded smoking/tobacco status to the index date was used for classification. All blood pressure measurements for each person were extracted, and the most recent daily systolic and diastolic blood pressures among all measurements for a person during the baseline data collection period was considered the baseline blood pressure. Laboratory tests were mapped to Logical Observation Identifiers Names and Codes. Per person, all laboratory values for eosinophil count, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, serum creatinine, glomerular filtration rate, and hemoglobin A1C were extracted. If an individual had multiple measurements during the extraction period for a specific laboratory value, then the value closest to January 1, 2006, was used for analysis. Comorbidities were ascertained using International Classification of Diseases (ICD), Ninth Revision (ICD-9) and Tenth Revision (ICD-10) diagnosis codes as recommended by the US Department of Health and Human Services, except for allergic rhinitis and chronic rhinosinusitis for which REP-defined ICD codes were used (see Table E1 in this article’s Online Repository at www.jaci-global.org).

**Exposure**

The exposure was the absolute eosinophil count. Per individual, all laboratory values for eosinophil count were extracted from January 1, 2001, to December 31, 2005. If an individual had multiple measurements during that time frame, then the value closest to January 1, 2006, was used for analysis. If an individual had more than 1 eosinophil count measurement on a given day, the values were aggregated by taking the mean.

**Outcomes**

Patients were followed from January 1, 2006, to December 31, 2020, to assess CVD outcomes, which included CHD, heart failure, stroke/transient ischemic attack, and CVD death. Only incident (first-ever) cases were included in the analysis. CHD as an outcome comprised any 1 of 3 distinct events that included myocardial infarction, unstable angina, or either coronary artery bypass graft surgery or percutaneous coronary intervention. MIs and unstable angina were identified using in-patient ICD-9 and ICD-10 codes. Coronary artery bypass graft surgery/percutaneous coronary intervention was identified using corresponding Current Procedural Terminology codes. Heart failure was identified using ICD codes that were used in the following contexts: first in-patient primary diagnosis, first primary discharge diagnosis, or 2 outpatient heart failure ICD codes more than 30 days apart. Stroke/transient ischemic attack and cardiovascular death were identified using ICD codes. The specific ICD codes used to define the CVD-related outcomes are listed in Table E1.

**Exclusion criteria**

Individuals who had a prevalent CVD (history of CVD before January 1, 2006) or who did not have any eosinophil measurements during the data extraction period were excluded from the study cohort.

**Statistical analysis**

The 2-sample t test (or Wilcoxon rank-sum test) for continuous variables and the chi-square test (or Fisher exact test) for categorical variables were
used to compare patient characteristics across the following groups: patients included in the study versus those excluded and males versus females. The 2-sample t test (or Wilcoxon rank-sum test) was used to compare eosinophil counts across groups. The association of patient characteristics with eosinophil count quartiles was assessed using ANOVA or the chi-square test as appropriate. Similarly, as a sensitivity analysis, eosinophil counts were subdivided into ranges that have been clinically used to stratify efficacy of biologics to treat severe eosinophilic asthma, and the association of these groups with patient characteristics was assessed using ANOVA or the chi-square test as appropriate.

Cox proportional hazards regression was used to investigate the association of incident CVD outcomes with eosinophil counts (cells \times 10^9/L). For each end point, 2 models were fit: model 1 adjusted for age, sex, and race; model 2 adjusted for age, sex, race, systolic blood pressure, diastolic blood pressure, total cholesterol, HDL cholesterol, diabetes, smoking, and hypertension treatment. To further supplement this analysis, multiple imputation was used to impute the missing eosinophil counts and covariates with 20 data sets imputed for each analysis and results were pooled using Rubin’s rule. An interaction between eosinophil counts and sex was assessed; stratified results were presented using Rubin’s rule. All analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Study population

We identified 76,128 individuals aged 30 years or older, who resided in Olmsted County, Minn, on January 1, 2006. Among these we excluded 5,317 individuals who had a prevalent CVD (history of CVD before January 1, 2006) and another 26,776 who did not have any eosinophil measurements during the data extraction period. Baseline characteristics comparing those who did and did not have the exposure (ie, eosinophil count) are summarized in Tables I and II. Those excluded because of missing exposure data were younger, more likely male and non-White, and less likely to have chronic disease. A summary of the demographic and clinical characteristics of the study cohort is presented in Table E2, A, and Table E2, B, overall and by sex, in this article’s Online Repository at www.jaci-global.org. Current and former smoking and tobacco use were more frequently seen in males. Among the chronic conditions identified, allergic rhinitis, asthma, and chronic rhinosinusitis were more prevalent in females. In contrast, hypertension, cardiac arrhythmias, hyperlipidemia, diabetes, and chronic kidney disease were more prevalent in males. In terms of allergic rhinitis and asthma specifically, the prevalences of allergic rhinitis (14.9%) and asthma (9.6%) in our study cohort were similar to those found in the United States where the prevalence of allergic rhinitis and asthma is 15% and 8%, respectively.

Blood eosinophil counts

The mean absolute eosinophil counts at baseline for several demographic and clinical characteristics are summarized in Table III overall and by sex. Overall, males had higher mean absolute eosinophil counts than females. Eosinophil counts were both age- and BMI-dependent, with increasing counts occurring with increasing age and BMI. This trend was observed in both males and females (see Figs E1 and E2 in this article’s Online Repository at www.jaci-global.org). Similarly, smoking and tobacco use (current and former) were also associated with higher absolute eosinophil counts. Among the multiple prevalent clinical conditions analyzed, the mean absolute eosinophil count was highest for individuals with asthma (mean absolute eosinophil count = 0.21 \times 10^9/L) followed by individuals with diabetes mellitus and chronic kidney disease (mean absolute eosinophil count = 0.19 \times 10^9/L in both).

Eosinophil counts were also subdivided into quartiles as presented in Tables IV and V. With each increase in quartile, there was a corresponding increase in mean age, mean BMI, frequency of current smoking and tobacco use, and mean triglyceride level. These trends were consistent in both males and females (see Tables E3 and E4 in this article’s Online Repository at www.jaci-global.org). Furthermore, the frequency of all clinical conditions studied also significantly increased with each rise in quartile. In all quartiles, females exhibited the highest frequency of allergic rhinitis, asthma, chronic rhinosinusitis, and COPD. In contrast, males had the highest frequency of hypertension, cardiac arrhythmias, hyperlipidemia, diabetes, chronic kidney disease, and cancer in all quartiles (Tables E3 and E4). In the sensitivity analyses,
TABLE II. Baseline characteristics by eosinophil assessment status

| Characteristic                  | Eosinophils not measured (n = 26,776) | Eosinophils measured (n = 44,035) | P value |
|--------------------------------|--------------------------------------|----------------------------------|---------|
| Systolic blood pressure (mm Hg) | 123.1 ± 16.8                         | 122.8 ± 17.1                     | .067    |
| Unknown, n                      | 7,165                                | 371                              |         |
| Diastolic blood pressure (mm Hg) | 74.7 ± 10.3                          | 73.1 ± 10.3                      | <.001   |
| Unknown, n                      | 7,165                                | 371                              |         |
| Total cholesterol (mg/dL)       | 196.7 ± 34.9                         | 194.7 ± 36.0                     | <.001   |
| Unknown, n                      | 15,344                               | 7,862                            |         |
| HDL cholesterol (mg/dL)         | 54.6 ± 16.0                          | 55.9 ± 16.6                      | <.001   |
| Unknown, n                      | 15,489                               | 8,359                            |         |
| LDL cholesterol (mg/dL)         | 115.7 ± 30.7                         | 112.0 ± 31.2                     | <.001   |
| Unknown, n                      | 15,587                               | 8,579                            |         |
| Triglycerides (mg/dL)           | 133.8 ± 80.5                         | 136.4 ± 88.2                     | .003    |
| Unknown, n                      | 15,499                               | 8,339                            |         |
| Creatinine (mg/dL)              | 1.05 ± 0.2                            | 1.02 ± 0.2                       | <.001   |
| Unknown, n                      | 19,571                               | 6,427                            |         |
| Glomerular filtration rate      | 68.3 ± 13.8                          | 68.1 ± 15.4                      | .257    |
| Unknown, n                      | 19,571                               | 6,427                            |         |
| HbA1c (%)                       | 6.2 ± 1.4                            | 5.9 ± 1.3                        | <.001   |
| Unknown, n                      | 25,559                               | 36,029                           |         |
| Allergic rhinitis               | 2,156 (8.1)                          | 6,578 (14.9)                     | <.001   |
| Asthma                          | 1,061 (4.0)                          | 4,215 (9.6)                      | <.001   |
| Chronic rhinosinusitis          | 1,877 (7.0)                          | 6,405 (14.6)                     | <.001   |
| COPD                            | 1,250 (4.7)                          | 5,533 (12.6)                     | <.001   |
| Hypertension                    | 3,167 (11.8)                         | 14,278 (32.4)                    | <.001   |
| Cardiac arrhythmias             | 1,059 (4.0)                          | 7,949 (18.1)                     | <.001   |
| Hyperlipidemia                  | 4,542 (17.0)                         | 16,814 (38.2)                    | <.001   |
| Diabetes mellitus               | 1,316 (4.9)                          | 6,040 (13.7)                     | <.001   |
| Chronic kidney disease          | 139 (0.5)                            | 1,852 (4.2)                      | <.001   |
| Cancer                          | 1,408 (5.3)                          | 7,374 (16.8)                     | <.001   |

Values are mean ± SD or count (%). HbA1c, Glycated hemoglobin.

the findings based on the clinical eosinophil cutoff points were consistent with that of quartiles (see Table E5 in this article’s Online Repository at www.jaci-global.org).

Blood eosinophil count and risk of CVD

There were 13,843 incident CVD events during the follow-up period including 2,519 CHD, 3,246 heart failure, and 6,302 stroke/transient ischemic attack (TIA) events, and 1,776 CVD deaths. Table VI summarizes the association between eosinophil counts and incident events for both the cohort with observed eosinophil counts and the complete cases analyses. In fully adjusted models, eosinophil counts were significantly associated with CHD (hazard ratio [HR], 1.44; 95% CI, 1.12-1.84), heart failure (HR, 1.62; 95% CI, 1.30-2.01), and for all CVDs (HR, 1.28; 95% CI, 1.12-1.46). Eosinophil levels were associated with stroke/TIA (HR, 1.37; 95% CI, 1.16-1.61) and CVD death (HR, 1.49; 95% CI, 1.10-2.00) in an age-, race/ethnicity-, and sex-adjusted model, but the association was attenuated with further adjustment for CVD risk factors (stroke/TIA [HR, 1.18; 95% CI, 1.00-1.40], CVD death [HR, 1.22; 95% CI, 0.90-1.67]). A sex-specific association was observed, with females having a higher risk than males for CHD (HR, 2.48 vs HR, 1.55, respectively; P = .027) in an age-, race/ethnicity-, and sex-adjusted model. In a fully adjusted model, a sex-specific association was observed, with males having a higher risk than females for CVD death (HR, 1.82 vs HR, 0.91, respectively; P = .015). Otherwise, no sex differences were observed for the other CVD events. These findings were consistent when considering only cases with complete covariate data (n = 29,168) and with that of the imputed data groups (see Table E6).

DISCUSSION

In a large general population–based cohort in the upper Midwest, we demonstrate that increased eosinophil counts correspond with increasing age, increasing BMI, and current/former smoking and tobacco use. Furthermore, we show that the prevalence of several chronic diseases, both atopic and nonatopic, increases as eosinophil counts increase. Finally, we also demonstrate that eosinophil counts are significantly associated with multiple CVD events including CHD, heart failure, stroke/TIA, and CVD death. Given our study’s retrospective, observational design, we were unable to account for steroid medication use, which may affect eosinophil counts, and thereby limit our findings. However, because corticosteroids would be expected to lower the eosinophil count, the use of corticosteroids would likely favor the null hypothesis.

Our results are consistent in several aspects with previous studies, which found eosinophil counts to be associated with several factors including being higher in males, in those with higher BMI, and in current/former smokers. Our finding that increased eosinophil counts correspond with increasing age may clarify associations between age and eosinophil counts, because previous studies have been mixed. Caspad et al analyzed data from the National Health and Nutrition Examination Surveys and noted that eosinophil counts increased with age in 34,181 individuals without asthma or COPD. This correlation was not observed in those with asthma or COPD. Hartl et al studied 11,042 random individuals in the general population in Austria and found no correlation between age and eosinophil counts in those 18 years and older. Mensinga et al performed a community-based population study including 3258 random individuals in the Netherlands and found that eosinophil counts actually decreased with increasing age. Differences in general populations, study methodology, and frequencies of comorbid conditions may explain these conflicting outcomes. Our study represents one of the largest in a general population to detail these clinical parameters in relation to eosinophil counts.

In addition to further defining demographic characteristics of eosinophil counts, our study investigated associations between eosinophil counts and several chronic diseases. Epidemiologic evidence for eosinophils’ roles in chronic diseases, other than atopic conditions, has been relatively limited, with previous studies demonstrating associations between eosinophil counts and cancer, hyperlipidemia, and hemoglobin A1c. In terms of cancer, a prospective study conducted by Andersen et al included 356,196 individuals from a primary care setting in Denmark. This study found that severe eosinophilia (defined as absolute eosinophil count ≥1.0 × 10^9/L) was associated with increased odds ratios (OR) for developing Hodgkin’s lymphoma (OR, 9.09), myeloproliferative neoplasms (OR, 3.87), and chronic lymphocytic leukemia (OR, 5.00). A cross-sectional analysis of 333,668 individuals in the UK Biobank by Tucker et al found that total, LDL, and non-HDL cholesterol were inversely associated with total eosinophil counts, whereas triglyceride levels were...
positively associated with eosinophil counts. A prospective cohort study performed by Amini et al. included 13,301 residents in the Netherlands and focused on eosinophil counts for metabolic and pulmonary traits. This study found positive associations between higher eosinophil counts and hyperlipidemia as well as higher hemoglobin A1C.

In our study, after dividing eosinophil counts into quartiles, we observed significant positive trends with several clinical factors and with multiple diseases. As eosinophil counts increased, the prevalence of allergic rhinitis, asthma, chronic rhinosinusitis, COPD, hypertension, cardiac arrhythmias, hyperlipidemia, diabetes mellitus, chronic kidney disease, and cancer all increased, providing support for a pathophysiologic role for eosinophils in these conditions. Mean values of blood pressure, total cholesterol, HDL and LDL cholesterol, triglycerides, serum creatinine, glomerular filtration rate, and hemoglobin A1c all increased as well with increasing eosinophil counts. Although these trends were statistically significant, likely due to the large sample size, the absolute changes were modest and may not be clinically significant. These significant, albeit incremental, differences may be indicative of eosinophils’ influence among several other factors in multiple metabolic pathways. In general, our study provides further epidemiologic evidence that eosinophils may play a pathophysiologic role in several chronic medical conditions beyond their well-established role in atopic diseases.
Finally, eosinophils have been investigated for their potential role in the inflammatory cascade of CVD. A number of studies have demonstrated associations between eosinophil counts with either CHD risk or worsened CVD outcomes. In contrast, other studies observed that higher eosinophil counts were associated with lesser degrees of coronary artery stenosis or were not associated with the prevalence of coronary artery disease at all. Moreover, fewer studies have addressed eosinophil counts in the general population in relation to incident CVD, as we investigated in our study.

One cohort study conducted in Japan that included 16,711 individuals and another cohort study performed in 4,615 males in Wales and England both found that a higher eosinophil count was associated with a higher incidence of CHD. These studies were limited by small size of incident events, narrow range of CVD end points, and limited populations. More recently, Shah et al used a large registry in England that included 775,231 individuals, aged 30 years or older without CVD at baseline, who had a median follow-up of 3.8 years. In the first 6 months, low eosinophil counts (defined as absolute eosinophil count = 0.05 x 10^9/L) were strongly associated with heart failure (HR, 2.05; 95% CI, 1.72-2.43), unheralded coronary death (HR, 1.94; 95% CI, 1.40-2.69), and ventricular arrhythmia/sudden cardiac death (HR, 3.05; 95% CI, 1.48-6.28). However, after 6 months, these associations were weak or null. There was lack of association with angina, nonfatal myocardial infarction, and stroke. In our study population of greater than 44,000 individuals, eosinophil counts were significantly associated with both CHD and heart failure. Our findings differ from those of Shah et al, and the greater influence of eosinophils on CVD that we observed may be due to our longer follow-up time for incident events and different statistical modeling methodology.

In total, our study provides compelling evidence for eosinophils having a potential role in the pathophysiology of CVD. The specific mechanisms by which eosinophils may promote CVD remain unclear, but a recent study suggests that eosinophils promote atherosclerotic plaque formation as well as thrombosis through platelet interactions and eosinophil extracellular traps. Furthermore, genetic variants influencing eosinophil numbers have been associated with MI. Additional epidemiologic studies with well-phenotyped cohorts followed longitudinally will provide further clinical and mechanistic insights into the role of eosinophils with CVD and other chronic diseases.

**Strengths and limitations**

Our study has several strengths including large population sample size, breadth and depth of longitudinal electronic health

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**TABLE IV. Quartiles of eosinophil counts (cells x 10^9/L) with chronic diseases**

| Characteristic                  | Quartile 1 (N = 12,679) | Quartile 2 (N = 10,357) | Quartile 3 (N = 10,214) | Quartile 4 (N = 10,785) | P value |
|---------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|---------|
| Eosinophil count range          | 0.09-0.09               | 0.09-0.13               | 0.13-0.21               | 0.21-3.50               | NA      |
| Age (y)                         | 50.3 ± 14.9             | 50.7 ± 14.1             | 53.2 ± 14.4             | 54.5 ± 15.1             | <.001   |
| BMI (kg/m^2)                    | 27.4 ± 5.8              | 28.5 ± 6.1              | 29.1 ± 6.2              | 29.4 ± 6.3              | <.001   |
| Current smoker                  | 1.140 (12.3)            | 1.109 (14.9)            | 1.506 (16.3)            | 1.740 (19.9)            | <.001   |
| Current tobacco user            | 1.144 (11.9)            | 1.172 (14.9)            | 1.540 (15.9)            | 1.742 (18.9)            | <.001   |
| Systolic blood pressure (mm Hg) | 121.3 ± 17.3            | 122.2 ± 17.0            | 123.5 ± 16.7            | 124.3 ± 17.2            | <.001   |
| Diastolic blood pressure (mm Hg)| 72.4 ± 10.2             | 73.2 ± 10.2             | 73.5 ± 10.2             | 73.3 ± 10.5             | <.001   |
| Total cholesterol (mg/dL)       | 193.2 ± 35.4            | 195.2 ± 36.0            | 195.8 ± 36.0            | 194.5 ± 36.4            | <.001   |
| HDL cholesterol (mg/dL)         | 58.8 ± 17.5             | 55.9 ± 16.3             | 55.0 ± 16.0             | 54.3 ± 16.3             | <.001   |
| LDL cholesterol (mg/dL)         | 110.1 ± 30.2            | 113.2 ± 31.3            | 113.0 ± 31.3            | 111.5 ± 31.7            | <.001   |
| Triglycerides (mg/dL)           | 123.5 ± 76.8            | 134.4 ± 96.6            | 140.7 ± 89.0            | 145.8 ± 87.6            | <.001   |
| Creatinine (mg/dL)              | 1.00 ± 0.22             | 0.99 ± 0.22             | 1.03 ± 0.26             | 1.05 ± 0.30             | <.001   |
| Glomerular filtration rate      | 68.4 ± 15.1             | 70.0 ± 16.0             | 67.5 ± 15.1             | 66.7 ± 15.5             | <.001   |
| HbA1c (%)                       | 5.8 ± 1.2               | 5.9 ± 1.3               | 6.0 ± 1.3               | 6.0 ± 1.2               | <.001   |

Values are mean ± SD.

HbA1c, Glycated hemoglobin; NA, not available/applicable.

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**TABLE V. Quartiles of eosinophil counts (cells x 10^9/L) and associated clinical characteristics**

| Characteristic                  | Quartile 1 (N = 12,679) | Quartile 2 (N = 10,357) | Quartile 3 (N = 10,214) | Quartile 4 (N = 10,785) | P value |
|---------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|---------|
| Eosinophil count range          | 0.09-0.09               | 0.09-0.13               | 0.13-0.21               | 0.21-3.50               | NA      |
| Allergic rhinitis               | 1,367 (12.5)            | 1,530 (14.4)            | 1,738 (14.9)            | 1,943 (18.0)            | <.001   |
| Asthma                          | 816 (7.4)               | 809 (7.6)               | 1,060 (9.1)             | 1,530 (14.2)            | <.001   |
| Chronic rhinosinusitis          | 1,449 (13.2)            | 1,647 (15.5)            | 1,653 (14.2)            | 1,656 (15.4)            | <.001   |
| COPD                            | 1,176 (10.7)            | 1,241 (11.7)            | 1,467 (12.6)            | 1,649 (15.3)            | <.001   |
| Hypertension                    | 2,927 (26.7)            | 3,111 (29.3)            | 4,065 (34.9)            | 4,175 (38.7)            | <.001   |
| Cardiac arrhythmias             | 1,953 (17.8)            | 1,750 (16.5)            | 2,092 (17.9)            | 2,154 (20.0)            | <.001   |
| Hyperlipidemia                  | 3,358 (30.6)            | 3,822 (36.0)            | 4,858 (41.7)            | 4,776 (44.3)            | <.001   |
| Diabetes mellitus               | 1,114 (10.2)            | 1,272 (12.0)            | 1,764 (15.1)            | 1,890 (17.5)            | <.001   |
| Chronic kidney disease          | 402 (3.7)               | 346 (3.3)               | 510 (4.4)               | 594 (5.5)               | <.001   |
| Cancer                          | 1,795 (16.4)            | 1,621 (15.2)            | 2,007 (17.2)            | 1,951 (18.1)            | <.001   |

Values are count (%).

NA. Not available/applicable.
record data, well-defined electronic clinical phenotypes, and comprehensive adjustment for potential confounders. Limitations of this study include its retrospective nature, which limits the inclusion of patients to those with available eosinophil count data and does not account for factors that may affect eosinophil counts such as concurrent acute illnesses, medications such as steroids, and the diurnal variation of eosinophil counts. 52 In addition, the use of ICD codes to solely determine the presence of diseases may lead to inaccuracies in disease counts. Selection bias may be present as well in those patients who had eosinophil count measurements performed, because indications for eosinophil count measurement may vary widely. In similar fashion, because this study was based on electronic health record data, other missing data occur, which may introduce bias. To address missingness, multiple imputation was performed, and the modeling results were very consistent across the complete data and imputed analysis. Finally, because our study was observational in design, residual confounding may occur, and we cannot reliably infer causality from our results.

Conclusions

In a large general population–based cohort, we demonstrate that increased eosinophil counts correspond with increasing age, increasing BMI, and current/former smoking and tobacco use. In addition, higher eosinophil counts are associated with a greater prevalence of several chronic nonatopic medical conditions, suggesting a greater role for eosinophils in human diseases. Finally, our study demonstrates that eosinophil counts are significantly associated with risk of CHD, heart failure, stroke/TIA, and CV death. Further prospective investigations will provide further evidence as to the utility of eosinophil counts as a biomarker for CVD risk.

Key messages

- Blood eosinophil counts are associated with several demographic factors including age, sex, BMI, and smoking status.
- Increased eosinophil counts may serve as an additional risk factor for CVDs in the general population.

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| TABLE VI. Association of eosinophil count and CVD |
|-----------------------------------------------|
| CVD categories | Cohort including only subjects with eosinophils measured (N = 44,035) | Cohort with complete cases only (N = 29,168) |
| No. of CHD events | 2,519 | 1,905 |
| Total person-years | 553,752 | 370,727.46 |
| Crude CHD rate, per 1,000 person-years | 4.55 | 5.14 |
| Time to CHD | | |
| Model 1, HR (95% CI) for eosinophils | 1.81 (1.44-2.29), <.001 | 1.76 (1.33-2.32), P < .001 |
| Model 2, HR (95% CI) for eosinophils | 1.44 (1.12-1.84), .004 | 1.35 (1.01-1.81), P = .045 |
| No. of HF events | 3,246 | 2,581 |
| Total person-years | 556,969 | 372,875.48 |
| Crude HF rate, per 1,000 person-years | 5.83 | 6.92 |
| Time to HF | | |
| Model 1, HR (95% CI) for eosinophils | 2.02 (1.65-2.49), <.001 | 2.21 (1.75-2.81), P < .001 |
| Model 2, HR (95% CI) for eosinophils | 1.62 (1.30-2.01), <.001 | 1.71 (1.33-2.19), P < .001 |
| No. of stroke/TIA events | 6,302 | 4,972 |
| Total person-years | 554,838 | 354,925.54 |
| Crude stroke/TIA rate, per 1000 person-years | 11.78 | 14.01 |
| Time to stroke/TIA | | |
| Model 1, HR (95% CI) for eosinophils | 1.37 (1.16-1.61), <.001 | 1.36 (1.12-1.64), P = .002 |
| Model 2, HR (95% CI) for eosinophils | 1.18 (1.00-1.40), .054 | 1.15 (0.95-1.40), P = .162 |
| No. of CVD death events<sup>a</sup> | 1,776 | 1,313 |
| Total person-years | 568,758 | 379,758.76 |
| Crude CV death rate, per 1,000 person-years | 3.12 | 3.46 |
| Time to CV death | | |
| Model 1, HR (95% CI) for eosinophils | 1.49 (1.10-2.00), .009 | 1.70 (1.21-2.39), P = .003 |
| Model 2, HR (95% CI) for eosinophils | 1.22 (0.90-1.67), .20 | 1.33 (0.93-1.91), P = .12 |
| No. of CVD events | 9,790 | 7,537 |
| Total person-years | 517,540 | 341,945.31 |
| Crude CVD rate, per 1,000 person-years | 18.9 | 22.04 |
| Time to CVD | | |
| Model 1, HR (95% CI) for eosinophils | 1.52 (1.34-1.73), <.001 | 1.51 (1.30-1.76), P < .001 |
| Model 2, HR (95% CI) for eosinophils | 1.28 (1.12-1.46), <.001 | 1.24 (1.06-1.45), P = .008 |

Model 1 = age, sex, race, and ethnicity.  
Model 2 = model 1 + systolic blood pressure, diastolic blood pressure, total cholesterol, HDL cholesterol, diabetes, smoking, and hypertension treatment.  
HF, Heart failure.  
<sup>a</sup>Patients who died outside of Minnesota have been censored at death.
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