RESEARCH ARTICLE

Association of the blood eosinophil count with hematological malignancies and mortality

Christen L. Andersen,[1,2*] Volkert D. Siersma,[2] Hans C. Hasselbalch,[1] Hanne Vestergaard,[3] Ruben Mesa,[4] Peter Felding,[5] Niels D.F. Olivarius,[2] and Ole W. Bjerrum[6]

Blood eosinophilia ($\geq$0.5 × 10^9/l) may be an early sign of hematological malignancy. We investigated associations between levels of blood eosinophils and risks of hematological malignancies and mortality in order to provide clinically derived cut-offs for referral to specialist hematology care. From the Copenhagen Primary Care Differential Count (*CopDiff*) Database, we identified 356,196 individuals with at least one differential cell count encompassing the eosinophil count during 2000–2007 and matched these laboratory data with Danish nationwide health registers. We used multivariable logistic regression to calculate odds ratios (ORs) for the 4-year incidences of hematological malignancies and mortality between the eosinophil counts and a reference count of 0.16 × 10^9/l which was the median eosinophil count in our data. Risks of hematological malignancies and mortality increased above the median eosinophil count. At the 99th percentile, corresponding to an eosinophil count of 0.75 × 10^9/l, risks of hematological malignancies were increased more than twofold with OR (95% C.I.) of 2.39 (1.91–2.99). Interestingly, risks reached a plateau around an eosinophil count of 1.0 × 10^9/l. Risks also increased when the eosinophil count approached zero. Here, counts associated relatively more with acute myeloid leukemia and myelodysplastic syndromes whereas counts above 0.16 × 10^9/l associated more with myeloproliferative neoplasms. Eosinophil counts associate with hematological malignancies and mortality even below the definition of eosinophilia. The observed plateau of risks around 1.0 × 10^9/l is important for physicians encountering patients with eosinophilia since even mild-to-moderate eosinophilia according to traditional definitions confers maximally increased risks of subsequent/subclinical hematological malignancy.
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Introduction

In healthy individuals, eosinophilic granulocytes (eosinophils) constitute <5% of all white blood cells [1]. Blood eosinophilia, traditionally defined for use in clinical practice as an eosinophil count of $\geq$0.5 × 10^9/l, is encountered in all areas of medicine and in both primary and secondary care. The degree of blood eosinophilia may be arbitrarily categorized as mild (from 0.5 × 10^9/l and up to 1.5 × 10^9/l), moderate (from 1.5 × 10^9/l and up to 5.0 × 10^9/l) and severe (from 5.0 × 10^9/l) and may arise from either clonal intrinsic disorders or from reactive extrinsic conditions [2–4]. Reactive causes account for the vast majority of cases. A plethora of distinct disease entities with concomitant eosinophilia has been known for many years, whereas the primary eosinophilic conditions were not introduced until 1968 [1,5,6]. Advances in cytogenetic, and in particular molecular techniques, have recently identified specific lymphoid and myeloid neoplasms with eosinophilia, hereby categorizing clonal markers in these entities [3,4,7]. For the prognostic evaluation and management of patients presenting with eosinophilia it is important to identify both the many patients with reactive eosinophilia and those patients with the rarer specific clonal diseases. This leaves a very small subgroup of patients with idiopathic hypereosinophilic syndrome [3,4,7,8], where neither clonality nor other primary stimuli can be demonstrated. Several useful algorithms for such workup have been presented and are used in clinical practice today [2–4].

Eosinophilia in routine blood samples has recently been demonstrated to be an early sign of both myeloid and lymphoid hematological malignancies [9], but the relation between the number of eosinophils and risks of such outcomes has not been investigated in large cohorts. Such knowledge might aid physicians managing patients with unexplained eosinophilia by providing clinically derived cut-offs for rational referral to specialist hematology care. The aim of this study is therefore to explore the associations between levels of blood eosinophils and risks of hematological malignancies and mortality.

Additional Supporting Information may be found in the online version of this article.

[1]Department of Hematology, Roskilde University Hospital, Roskilde, Denmark; [2]The Research Unit for General Practice and Section of General Practice, Department of Public Health, University of Copenhagen, Copenhagen, Denmark; [3]Department of Hematology, Odense University Hospital, Odense, Denmark; [4]Division of Hematology and Medical Oncology, Mayo Clinic Cancer Center, Scottsdale, USA; [5]The Elective Laboratory of the Capital Region, Copenhagen, Denmark; [6]Department of Hematology, Copenhagen University Hospital, Copenhagen, Denmark.

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***Correspondence to:** Christen Lykkegaard Andersen M.D. Ph.D., Department of Hematology, Roskilde University Hospital, Koegevej 7, 4000 Roskilde, Denmark. E-mail: christenla@gmail.com
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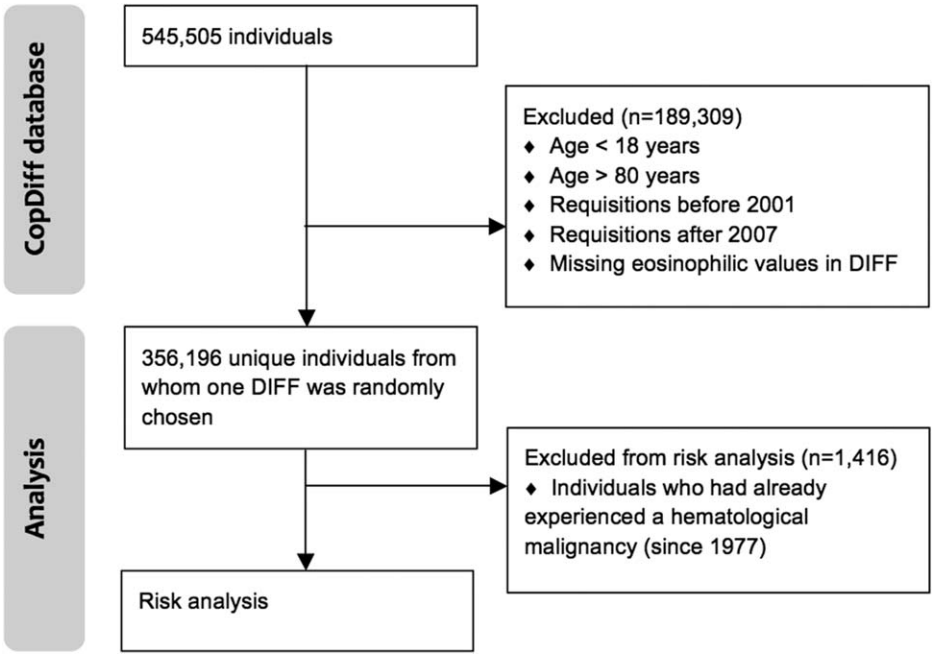

Figure 1. Flowchart. CopDiff, Copenhagen primary care differential count database; DIFF, differential cell count.

Using a primary care resource, comprising data from almost 360,000 individuals, we assessed the risks of emerging hematological malignancies as well as mortality, in the 4 years following differential blood cell count sampling. By matching these laboratory data with Danish nationwide health registers, risk estimates for the outcomes were assessed.

Methods

Subjects. The Copenhagen General Practitioners' Laboratory (CGPL) (since January 1, 2013 The Elective Laboratory of the Capital Region) is the only laboratory for general practitioners (GPs) in the Copenhagen area covering ~1.2 million inhabitants. CGPL has International Organization for Standardization (ISO) accreditation and has registered all analytical results since May 1, 2000. The Copenhagen Primary Care Differential Count (*CopDiff*) database contains results from all differential cell counts (DIFFs) requested by GPs in Copenhagen from July 1, 2000 to January 25, 2010. The *CopDiff* database has recently been reviewed in detail [10]. From 545,505 individuals, we included all adults (aged 18–80 years) with at least one DIFF in the period January 1, 2001 to December 31, 2007 ($n = 359{,}950$). From each individual, a single DIFF encompassing the eosinophil count was randomly chosen by computer-generated numbers and called the index DIFF ($n = 356{,}196$; 3,754 individuals were missing a valid eosinophil count), Fig. 1. We found that our strategy of randomly choosing one DIFF per individual to assess incidences of the below-specified outcomes was feasible for two reasons. First, it avoids having to adjust for repeated measurements of the same individual at different points in time. Second, we sought to minimize surveillance bias which seemed more likely to occur if, for example, we had opted for "the first DIFF" or "the DIFF closest to the outcome of interest." Eosinophil test results reported as "$<0.02 \times 10^9$/l" were set to "0.0×10^9/l" in order to maintain only numeric values in the database ($n = 1{,}889$). Where available, the level of C-reactive-protein (CRP), categorized as "increased" (≥ 10 mg/$n = 48.349$) vs. "normal" (<10 mg/$n = 181.162$) was also obtained from the same index requisitions as the index DIFF. We used this information as a surrogate marker for ongoing increased inflammation, i.e. a potential confounder, when performing risk analysis. We did this by adjusting for CRP levels by adding a three-category CRP variable (categories: "normal," "increased," "measurement not obtained") as a covariate to the logistic regression models.

Exclusions. We assessed whether a previous DIFF ($n = 32{,}475$) existed in the *CopDiff* database for every included individual in a 6-month period before the randomly chosen index DIFF. We found this information relevant since previous DIFFs from not too long before the index DIFF would imply that the index DIFF was part of a monitoring initiative thereby rendering a previous DIFF (with or without eosinophilia) a potential confounder. Therefore, and since the *CopDiff* database started July 1, 2000, we excluded DIFFs before January 1, 2001 in order to be able to perform this assessment for all included individuals (Figs. 1 and 2). Also, in order to be able to associate the eosinophil counts to the selected outcomes with a reasonable certainty, we decided that all individuals were to have a fixed 4-year follow up after the index DIFF and since the cut-off date in Danish registers for the purposes of our study was January 1, 2012, we excluded DIFFs after December 31, 2007 (Fig. 1 and 2). To assess only *de novo* cases of hematological malignancies, individuals who had already experienced a hematological malignancy at time of index DIFF sampling (and since 1977) were excluded from risk analyses.

Analytical methods of the CopDiff database. All DIFF samples were analyzed on Siemens® (Bayer®/Technicon®) hematology systems. The CGPL used three similar types of these instruments in the period 2000–2010 which in chronological order were Technicon® H3 RTX (used between 2000 and 2002), ADVIA® 120 (used between 2002 and 2010) and ADVIA® 2120i (used together with ADVIA® 120 from 2009 to 2010). The basic chemical and physical methods are identical among these systems. Samples were subjected to microscopic (manual) differential cell counting of leukocyte types if flagged for this during the initial automated differential counting (1.38%). When switching from H3 RTX to ADVIA 120 there was a relative drop of 5% in "Red cell distribution width" analyses and no other changes in hematological analyses in the *CopDiff* period (2000–2010) were performed.

Registries. The *CopDiff* database is linked to the following three nationwide registers: (i) The Danish Civil Registration System (CRS), giving information on vital status and issuing everyone living in Denmark with a permanent and unique personal identification number, which enables linkage between study populations and all national registries [11]; (ii) the Danish Cancer Registry (DCR), containing data on all malignancies in Denmark since 1942 and to which reporting is mandatory [12]; and (iii) The Danish National Patient Register (NPR) which has recorded information on all contacts since 1977 with hospitals in Denmark, including discharge diagnoses, outpatient clinic contacts and surgical procedures performed; and to which reporting is also mandatory [13]. The Danish nationwide health registers are continuously updated with patient data and the cut-off date for the purposes of our study was January 1, 2012. We computed Charlson's Comorbidity Index (CCI) [14] from the hospital contacts recorded in the NPR for 3 years before the index DIFF in order to be able to adjust for possible confounding by comorbid conditions. CCI is a weighted sum of a broad selection of prevalent diagnoses from hospital contacts recorded in the NPR for 3 years before the index ANC. These diagnoses were originally chosen to reflect mortality risk.

Outcomes. Outcomes were incidences of "All hematological cancer" (taken from the DCR), as defined by the International Classification of Diseases version 10 (ICD-10) over the 4-year period following the DIFF, and "All-cause mortality" (taken from the CRS). Please refer to the Supporting Information for details on these entities (Supporting Information Table I). The study was approved by The Danish Data Protection Agency (journal no: 2013-54-0507), and did not need approval by an institutional review board or ethical review board according to Danish legislation. Patient information was anonymized and de-identified prior to analysis and no clinical records were used. Patient consent is not mandatory for this type of study in Denmark.

Statistical analysis. We used multivariable logistic regression to calculate the odds ratios (ORs) for the 4-year incidences of the outcomes between eosinophil counts and a reference count of 0.16×10^9/l which was the median eosinophil

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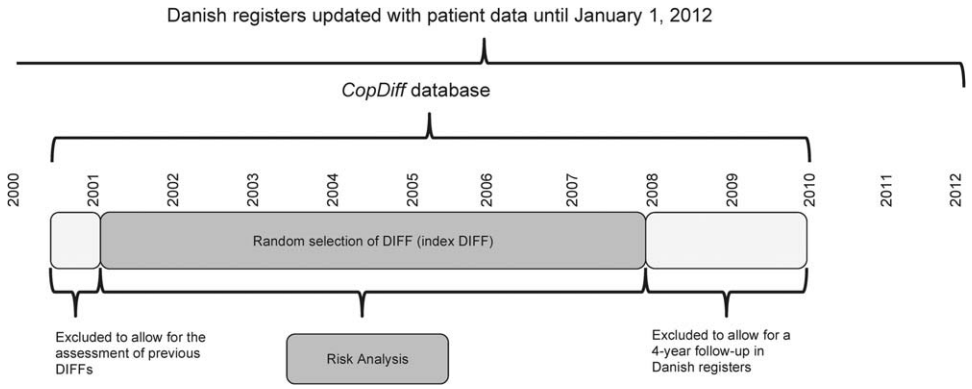

Figure 2. Timeline illustrating the period from which differential cell counts were selected from the *CopDiff* database. DIFF, differential cell count.

TABLE I. Odds Ratios (ORs) for the 4-year Incidence of "All Hematological Cancer" and "All-Cause Mortality" for Selected Percentiles

		All hematological cancer				All-cause mortality			
			95% C.I.				95% C.I.		
Percentile	Eosinophils (10^9/l)	Odds ratio	Lower	Upper	*P* value	Odds ratio	Lower	Upper	*P* value
0.1%	0.00	10.68	8.60	13.27	<0.001	2.79	2.56	3.03	<0.001
0.5%	0.00	10.68	8.60	13.27	<0.001	2.79	2.56	3.03	<0.001
1%	0.02	6.10	5.18	7.18	<0.001	2.22	2.08	2.36	<0.001
2%	0.03	4.64	4.05	5.33	<0.001	1.99	1.88	2.10	<0.001
5%	0.05	2.83	2.57	3.13	<0.001	1.62	1.56	1.68	<0.001
10%	0.07	1.92	1.79	2.06	<0.001	1.38	1.34	1.41	<0.001
25%	0.10	1.30	1.24	1.36	<0.001	1.16	1.14	1.18	<0.001
50%	0.16	1.00	ref	ref	ref	1.00	ref	ref	ref
75%	0.26	1.35	1.22	1.49	<0.001	1.05	1.02	1.08	<0.001
90%	0.38	1.68	1.48	1.91	<0.001	1.11	1.07	1.16	<0.001
95%	0.47	1.74	1.47	2.07	<0.001	1.14	1.08	1.20	<0.001
98%	0.62	1.97	1.58	2.45	<0.001	1.22	1.14	1.30	<0.001
99%	0.75	2.39	1.91	2.99	<0.001	1.35	1.25	1.45	<0.001
99.5%	0.91	3.16	2.39	4.17	<0.001	1.55	1.39	1.72	<0.001
99.9%	1.63	5.16	3.44	7.76	<0.001	1.93	1.64	2.27	<0.001

Values are percentiles, eosinophil counts, odds ratios, 95% confidence intervals and *P* values for the defined outcomes from multivariable logistic regression analysis and adjusted for sex, age, year, and month of DIFF sampling, CRP, previous DIFF sampling and Charlson's Comorbidity Index.

count in our data. These ORs were adjusted for known and possible confounders such as sex, age, year, and month of DIFF sampling, CRP (as a surrogate marker for increased inflammation), previous DIFF sampling and competing comorbid conditions (CCI), and modeled as a restricted cubic spline [15]. The potential confounders were included as additional variables in the logistic regression models. Age was the only continuous variable and, additional to the continuous age variable, age-squared was added to the logistic regression models to account for possible non-linearity for this covariate. Interactions of eosinophils (the splines) with sex and age (in three categories) were investigated, but no significant interactions were seen. The percentiles given in tables are from the unstratified data. The ORs are the adjusted ORs obtained from the splines together with the confidence intervals read from the splines at the corresponding point estimate. The Chi-squared test was used for comparison of the observed distributions of incident disease between the eosinophil groups of "$<0.16 \times 10^9$/l" and "$\geq 0.16 \times 10^9$/l." All analyses and calculations were performed with SAS version 9.2 (SAS Institute, Cary, NC) and restricted cubic splines as implemented in the R (version 3.1.1) package "rcs" with knots: 0.01, 0.05, 0.25, 0.50, 1.00, 1.50.

Results

In the full cohort of 359,950 individuals there was a female/male sex ratio of 1.38 (208,691/151,259) and a mean age (SD) of 48.3 (16.7) years. Of these, 14,406 individuals (4%) had eosinophilia ($\geq 0.5 \times 10^9$/l). Compared with the reference count of 0.16×10^9/l, risks for hematological malignancies and mortality were increased both above and below the definition of blood eosinophilia (Table I). At the 99th percentile, corresponding to an eosinophil count of 0.75×10^9/l, risks of hematological malignancies were increased more than twofold with OR (95% C.I.) of 2.39 (1.91–2.99), $P < 0.001$.

Furthermore, risks of hematological malignancies and mortality also increased when eosinophil count was below the median. This effect was most pronounced in hematological malignancies where risks increased sixfold in the 1st percentile (corresponding to an eosinophil count of 0.02×10^9/l) with an OR of 6.10 (5.18–7.18, $P < 0.001$).

To illustrate this nonlinear relationship, we modeled restricted cubic splines of the ORs for the outcomes according to the eosinophil count (Figs. 3 and 4). The risk curves were U-shaped for both outcomes, and the median eosinophil count of 0.16×10^9/l represented the lowest risk. In addition, risks reached a plateau at an eosinophil count around 1.0×10^9/l, above which the risks did not increase noticeably. To focus on the role of manual DIFFs in these risk associations, we repeated the analyses after having omitted manual counts. The same nonlinear relationship (U-shaped curves) was evident, however, associations were less strong (Supporting Information Table II and Supporting Information Figs. 1 and 2).

We then compared incident diagnoses below and above the median eosinophil count of 0.16×10^9/l for hematological malignancies, in an attempt to shed light on the mechanisms behind the observed increases in risk for low eosinophil counts (Table II). Overall, the distributions differed significantly ($P < 0.001$) and eosinophil counts below 0.16×10^9/l associated relatively more with acute myeloid leukemia (11.8% vs.

6.6%) and myelodysplastic syndromes (12.3% vs. 3.6%) as opposed to eosinophil counts above 0.16 × 10^9/l which associated more to myeloproliferative neoplasms (10.1% vs. 2.6% for polycythemia vera and 9.8% vs. 4.4% for systemic mastocytosis, essential thrombocythemia and unspecified myeloproliferative disease).

Lastly, in order to provide more data regarding the time lag between the index DIFFs and subsequent diagnosis of disease, we repeated analyses after having omitted individuals with events in the first year after the index DIFF from the analyses. Risk associations for the low eosinophil counts were now less strong whereas they disappeared above the threshold of 0.5 × 10^9/l for hematological malignancies (Supporting Information Table III and Supporting Information Figs. 3 and 4).

Discussion

In this study of almost 360,000 individuals, we observe that eosinophilia (≥0.5 × 10^9/l) is a relatively common phenomenon in routine blood samples (4%). We also demonstrate that eosinophil numbers associate with the subsequent diagnosis of malignant hematological disease and mortality, even below the definition of blood eosinophilia, and that these risks reach a plateau around ∼1.0 × 10^9/l.

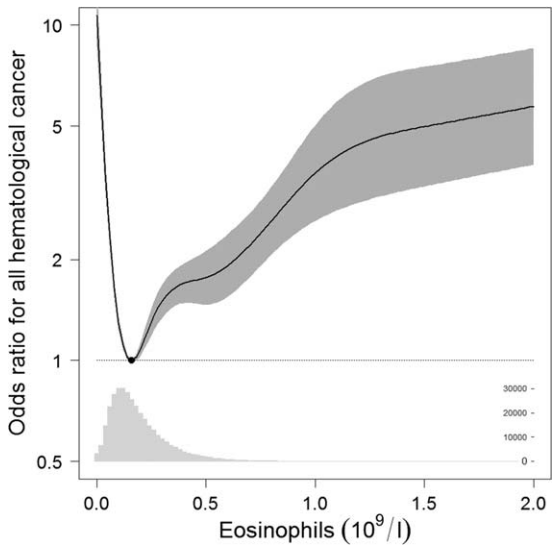

Figure 3. Odds ratio (OR) for the 4-year incidence of hematological malignancies. Odds ratio for the indicated eosinophil count compared to a reference count of 0.16 × 10^9/l. The shaded area around the line denotes the 95% confidence interval. The histogram at the bottom of the figure denotes the distribution of the 356,196 eosinophil counts in the data.

The observed plateau of risks for hematological cancer is important for physicians who manage patients with unexplained eosinophilia, since even mild-to-moderate eosinophilia (as defined above) confers maximally increased risks of subsequent/subclinical hematological malignancy. Such patients may be considered for referral to specialist hematology care.

Analyses share the U-shaped dose-response relationship, also termed *hormesis* [16]. Eosinophil counts above the nadir of our U-shaped curves (i.e., the median eosinophil count of 0.16 × 10^9/l) associated more to myeloproliferative neoplasms than did counts below the median which would be in accordance with what is known from clinical hematology; that an increased number of eosinophils are present to a varying extent as part of these clonal diseases, in particular in polycythaemia vera [17]. Conversely, an association of low (<0.16 × 10^9/l) eosinophil counts with the subsequent diagnoses of acute myeloid leukemia and myelodysplastic syndromes may be explained by the defective production of mature granulocytes *per se* which is the hallmark of these diseases entities. Concurrent increases in risk of mortality at low eosinophil counts correlate well with the seriousness of these latter conditions. We observed that risk associations were less strong (albeit still statistically significant) when omitting the small fraction of manual DIFFs from analyses. This complies with clinical experience; DIFFs flagged for manual counting exhibit pathologies to a greater extent than purely automated DIFFs.

When scrutinizing the time lag between the index DIFFs and subsequent diagnosis by omitting the individuals who were diagnosed in the first year after index DIFF sampling, we also observed that risk associations for the low eosinophil counts were less strong. This finding likely reflects that patients with MDS and, to a greater extent, acute leukemia are symptomatic or at least more promptly referred to secondary care. Interestingly, we also noted that risk associations above the threshold level of blood eosinophilia disappeared. This observation may mirror the referral behavior of the GPs where patients with abnormal blood values *per se* are more likely to be promptly referred.

This study has several limitations. First, we did not have information about drug treatment. Various types of drugs are known to cause eosinophilia [2] whereas others, especially steroids, are known to induce eosinophilic apoptosis [18]. However, steroid use has not been

TABLE II. The distribution of incident cases of disease (within 4 years from index DIFF) in eosinophil groups

Type	Eosinophils <0.16 × 10^9/l (*n*)	Percent within group	Eosinophils ≥0.16 × 10^9/l (*n*)	Percent within group
Hematological cancer, individuals at risk = 354,780[a]				
Hodgkin lymphoma	31	4.4%	58	7.4%
Non-Hodgkin lymphoma	231	33.0%	242	31.0%
Malignant immunoproliferative diseases including multiple myeloma	106	15.1%	117	15.0%
Acute lymphoblastic leukemia	11	1.6%	3	0.4%
Chronic lymphatic leukemia	91	13.0%	104	13.3%
Acute myeloblastic leukemia	83	11.8%	52	6.6%
Chronic myelomonocytic leukemia	3	0.4%	2	0.3%
Chronic myeloid leukemia	10	1.4%	19	2.4%
Histiocytosis X, multisystemic	0	0%	1	0.1%
Polycythemia vera	18	2.6%	79	10.1%
Myelodysplastic syndromes	86	12.3%	28	3.6%
Systemic mastocytosis, unspecified myeloproliferative disease and essential thrombocythemia	31	4.4%	77	9.8%
Total, $P < 0.001$[b]	701	100.0%	782	100.0%

[a] To assess only *de novo* cases of hematological malignancies, individuals who had already experienced a hematological malignancy (since 1977) were excluded from analyses, please refer to Fig. 1 for details.
[b] Chi-squared test for the overall comparison of distributions between the groups.

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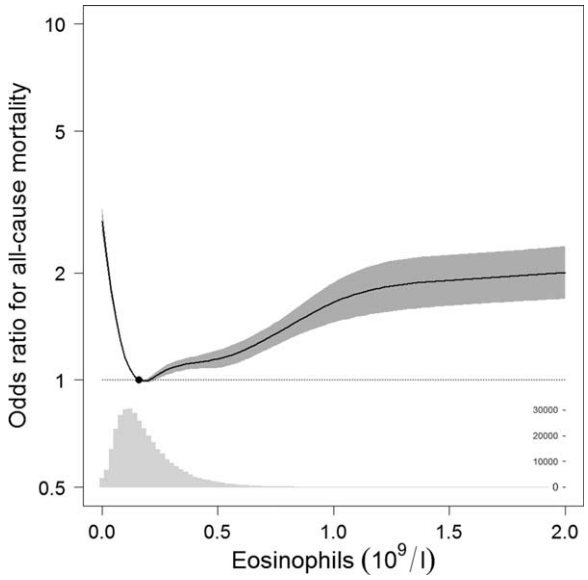

Figure 4. Odds ratio (OR) for the 4-year incidence of all-cause mortality. Odds ratio for the indicated eosinophil count compared to a reference count of 0.16 × 10^9/l. The shaded area around the line denotes the 95% confidence interval. The histogram at the bottom of the figure denotes the distribution of the 356,196 eosinophil counts in the data.

reported to affect risks of *de novo* hematological malignancy thereby limiting a potential confounding effect on these specific outcomes. On the other hand, comorbid conditions for which drugs, including steroids, may be given can confound our results. Therefore, we implemented the Charlson's Comorbidity Index in the risk analyses. Second, the NPR only holds information on individuals who have been in contact with secondary care and therefore patients exclusively managed in primary care are not included in the present analyses. Third, we did not have access to clinical information about the patients, such as weight, smoking, alcohol consumption, exercise patterns, and family history of disease. These are associated with several types of solid cancer. The relation of these clinical variables to hematological malignancies and the eosinophil count is less clear and not examined in detail [19,20], or do not show any major direct association [21].

The *CopDiff* database also has some important strengths. First, access to all DIFFs from all GPs on some 360,000 individuals from the Copenhagen area over a 7-year period offers a unique insight from a population sample that covers ~20% of the entire population of Denmark. Second, all diagnoses in this study were derived from the DCR and the NPR, which were established in 1942 and 1977, respectively, and to which reporting is mandatory. Validity of both registers is secured through quality control routines applied in the daily production and completion of annual reports [12,13]. Third, The *CopDiff* database comes from a population which can be assumed to exhibit disease to a greater extent than the general population. The use of logistic regression analysis on the 4-year incidence ensures that measures of excess risk (OR) can be interpreted independently of the frequency of the outcomes in the study. The OR therefore seems a valid estimate for excess risk in the general population as well [22].

In conclusion, this study demonstrates that eosinophil numbers associate with malignant hematological disease and mortality, even below the definition of blood eosinophilia. These associations are U-shaped as low levels also associate to the outcomes. Importantly, the curves describing the association between the eosinophil count and the outcomes level off around 1.0 × 10^9/l, beyond which risks do not seem to increase noticeably. These are important observations for physicians encountering patients with eosinophilia.

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Author Contribution

CLA co-designed the study, collected, analyzed and interpreted data and drafted the manuscript. VS analyzed and interpreted data and performed the statistical analyses. HCH, HV, PF and RM analyzed and interpreted data. NdFO and OWB co-designed the study, collected, analyzed and interpreted data. All authors revised the manuscript critically for important intellectual content, and approved the final version to be submitted.

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