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Association between blood eosinophil count and risk of readmission for patients with asthma: historical cohort study

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Association between blood eosinophil count and risk of readmission for patients with asthma: historical cohort study --Manuscript Draft--

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Article Type:	Research Article
Full Title:	Association between blood eosinophil count and risk of readmission for patients with asthma: historical cohort study
Short Title:	Blood eosinophil count and risk of readmission for asthma
Corresponding Author:	David B Price Observational & Pragmatic Research Institute Paya Lebar Square, SINGAPORE
Keywords:	asthma; eosinophils; hospitalization; patient readmission
Abstract:	<p>Background Recent studies have demonstrated an association between high blood eosinophil counts and greater risk of asthma exacerbations. We sought to determine whether patients hospitalized for an asthma exacerbation were at greater risk of readmission if they had a high blood eosinophil count documented before the first hospitalization.</p> <p>Methods This historical cohort study drew on 2 years of medical record data (Clinical Practice Research Datalink with Hospital Episode Statistics linkage) of patients (aged ≥ 5 years) admitted to hospital in England for asthma, with recorded blood eosinophil count within 1 baseline year before admission. We analyzed the association between high blood eosinophil count ($\geq 0.35 \times 10^9$ cells/L) and readmission risk during 1 year of follow-up after hospital discharge, with adjustment for predefined, relevant confounders using forward selection.</p> <p>Results We identified 2,613 eligible patients with asthma-related admission, of median age 51 years (interquartile range, 36-69) and 76% women (1,997/2,613). Overall, 835/2,613 (32.0%) had a preadmission high blood eosinophil count. During the follow-up year, 130/2,613 patients (5.0%) were readmitted for asthma, including 55/835 (6.6%) with vs. 75/1,778 (4.2%) without high blood eosinophil count at baseline (adjusted hazard ratio [HR] 1.49; 95% CI 1.04-2.13, $p=0.029$). The association was strongest in never-smokers ($n=1,296$; HR 2.16, 95% CI 1.27-3.68, $p=0.005$) and absent in current smokers ($n=547$; HR 1.00, 95% CI 0.49-2.04, $p=0.997$).</p> <p>Conclusions A high blood eosinophil count in the year before an asthma-related hospitalization is associated with increased risk of readmission within the following year. These findings suggest that patients with asthma and preadmission high blood eosinophil count require careful follow-up, with treatment optimization, after discharge.</p>
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<p>Financial Disclosure</p> <p>Please describe all sources of funding that have supported your work. This information is required for submission and will be published with your article, should it be accepted. A complete funding statement should do the following:</p> <p>Include grant numbers and the URLs of any funder's website. Use the full name, not acronyms, of funding institutions, and use initials to identify authors who received the funding.</p> <p>Describe the role of any sponsors or funders in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. If the funders had no role in any of the above, include this sentence at the end of your statement: "<i>The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.</i>"</p> <p>However, if the study was unfunded, please provide a statement that clearly indicates this, for example: "<i>The author(s) received no specific funding for this work.</i>"</p> <p>* typeset</p>	<p>Data acquisition and analyses were funded by AstraZeneca. This was a collaborative study. Employees of the sponsor were part of the study steering committee and participated in the study design. All authors, including those employed by AstraZeneca, participated in the data interpretation, decision to publish, and preparation of the manuscript.</p>
<p>Competing Interests</p> <p>You are responsible for recognizing and disclosing on behalf of all authors any competing interest that could be perceived to bias their work, acknowledging all financial support and any other relevant financial or non-financial competing interests.</p> <p>Do any authors of this manuscript have competing interests (as described in the PLOS Policy on Declaration and Evaluation of Competing Interests)?</p>	<p>I have read the journal's policy and the authors of this manuscript have the following competing interests:</p> <p>MK is an employee of the Observational and Pragmatic Research Institute Pte LTD, which conducted this study and which has conducted paid research in respiratory disease on behalf of the following other organizations in the past 5 years: Aerocrine; AKL Ltd.; Almirall; AstraZeneca; British Lung Foundation; Boehringer Ingelheim; Chiesi; GlaxoSmithKline; Mylan; Mundipharma; Napp; Novartis; Orion; Respiratory Effectiveness Group; Takeda; Teva; and Zentiva, a Sanofi company.</p> <p>JN is an employee, and TNT, GG, and SR are employees and shareholders of AstraZeneca, which supplied the funding for this study.</p> <p>MvdB has, within the last 5 years, received research grants paid to the University of Groningen from AstraZeneca, GlaxoSmithKline, Teva, and Chiesi.</p> <p>GB has, within the last 5 years, received honoraria for lectures from AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Pfizer, and Teva; he is a member of advisory boards for AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, Sanofi/Regeneron, and Teva.</p> <p>RJ reports grants, personal fees and non-financial support from Astra Zeneca,</p>

<p>If yes, please provide details about any and all competing interests in the box below. Your response should begin with this statement: <i>I have read the journal's policy and the authors of this manuscript have the following competing interests:</i></p> <p>If no authors have any competing interests to declare, please enter this statement in the box: <i>"The authors have declared that no competing interests exist."</i></p> <p>* typeset</p>	<p>personal fees from Boehringer Ingelheim, personal fees from Chiesi, personal fees and non-financial support from GSK, grants and personal fees from Novartis, non-financial support from Nutricia, personal fees from Pfizer, outside the submitted work.</p> <p>JWHK reports grants and personal fees from AstraZeneca, grants and personal fees from Boehringer Ingelheim, grants from Chiesi, grants and personal fees from GSK, grants and personal fees from Novartis, grants from Mundi Pharma, grants from TEVA, outside the submitted work.</p> <p>AMG has attended advisory boards for Glaxo SmithKline, Novartis, AstraZeneca, Boehringer Ingelheim andTeva. He has received speaker fees from Novartis, AstraZeneca, Vectura, Boehringer Ingelheim and Teva. He has participated in research with Hoffman La Roche, GlaxoSmithKline and Boehringer Ingelheim. He has attended international conferences sponsored by AstraZeneca and Boehringer Ingelheim. He has consultancy agreements with AstraZeneca and Vectura.</p> <p>IDP has received speaker's honoraria for speaking at sponsored meetings from AstraZeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, and GSK and a payment for organising an educational event for SPRs from AZ. He has received honoraria for attending advisory panels with Almirall, Genentech, Regeneron, AstraZeneca, Boehringer Ingelheim, GSK, MSD, Schering-Plough, Novartis, Dey, Napp and Respivert. He has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GSK, AstraZeneca and Napp.</p> <p>DBP has board membership with Aerocrine, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals; consultancy agreements with Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Napp, Novartis, Pfizer, Teva Pharmaceuticals, and Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from Aerocrine, AKL Research and Development Ltd, AstraZeneca, Boehringer Ingelheim, British Lung Foundation, Chiesi, Mylan, Mundipharma, Napp, Novartis, Pfizer, Respiratory Effectiveness Group, Teva Pharmaceuticals, Theravance, UK National Health Service, Zentiva; payment for lectures/speaking engagements from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Merck, Mundipharma, Novartis, Pfizer, Skyepharma, and Teva Pharmaceuticals; payment for manuscript preparation from Mundipharma and Teva Pharmaceuticals; payment for the development of educational materials from Mundipharma and Novartis; payment for travel/accommodation/meeting expenses from Aerocrine, AstraZeneca, Boehringer Ingelheim, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals; funding for patient enrolment or completion of research from Chiesi, Novartis, Teva Pharmaceuticals, and Zentiva; stock/stock options from AKL Research and Development Ltd which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); and is peer reviewer for grant committees of the Efficacy and Mechanism Evaluation programme, and Health Technology Assessment.</p>
<p>Ethics Statement</p> <p>You must provide an ethics statement if your study involved human participants, specimens or tissue samples, or vertebrate animals, embryos or tissues. All information entered here should also be included in the Methods section of your manuscript. Please write "N/A" if your study does not require an ethics statement.</p> <p>Human Subject Research (involved</p>	<p>The study was performed in compliance with all applicable local and international laws and regulations and to standards suggested for observational studies. The study protocol was approved by the CPRD Independent Scientific Advisory Committee (ISAC approval number 16_236) and registered with the European Union electronic Register of Post-Authorisation Studies (EU PAS Register number EUPAS15869). No patient identifying information was accessible during the study.</p>

human participants and/or tissue)

All research involving human participants must have been approved by the authors' Institutional Review Board (IRB) or an equivalent committee, and all clinical investigation must have been conducted according to the principles expressed in the [Declaration of Helsinki](#). Informed consent, written or oral, should also have been obtained from the participants. If no consent was given, the reason must be explained (e.g. the data were analyzed anonymously) and reported. The form of consent (written/oral), or reason for lack of consent, should be indicated in the Methods section of your manuscript.

Please enter the name of the IRB or Ethics Committee that approved this study in the space below. Include the approval number and/or a statement indicating approval of this research.

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Additional data availability information:

RE: PONE-D-18-12337

Stelios Loukides
Academic Editor

Dear Dr. Loukides:

Thank you for the review of our manuscript and for giving us the opportunity to provide a revision.

As instructed, we have resubmitted the following items, each as a separate file:

- A rebuttal letter that responds to each point raised by you and the reviewers, labeled 'Response to Reviewers'
- A marked-up copy of our manuscript that highlights changes made to the original version, labeled 'Revised Manuscript with Track Changes'
- An unmarked version of our revised paper without tracked changes, labeled 'Manuscript'

In addition, we have ensured that our revised manuscript meets *PLOS ONE's* style requirements, including those for file naming.

Finally, as requested, we have included further details below on sharing the de-identified data set and an updated Funding Statement. The updated Competing Interests Statement follows my signature. Thank you for changing the online submission form on our behalf.

Data sharing restrictions

The dataset supporting the conclusions of this article was derived from the Clinical Practice Datalink (CPRD; <http://www.cprd.com>) and linked Hospital Episode Statistics (<http://content.digital.nhs.uk/hes>). The study protocol was approved by the CPRD Independent Scientific Advisory Committee (ISAC approval number 16_236). We do not have permission to give public access to these datasets; however, researchers may request access for their own purposes.

Funding Statement

Data acquisition and analyses were funded by AstraZeneca. This was a collaborative study involving both employees of the sponsor and an independent steering committee. The funder of the study participated in the study design, decision to publish, and preparation of the manuscript. In addition, the funder provided support in the form of salaries for authors TNT, GG, JN, and SR. Employees of the sponsor were part of the study steering committee and participated in the study design. All authors, including those employed by AstraZeneca, participated in the data interpretation, decision to publish, and preparation of the manuscript. All authors had full access to study results and had final responsibility for the decision to submit for publication. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

Yours sincerely,

David Price, for the authors

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Competing Interests Statement

I have read the journal's policy and the authors of this manuscript have the following competing interests:

MK is an employee of the Observational and Pragmatic Research Institute Pte Ltd, which conducted this study and which has conducted paid research in respiratory disease on behalf of the following other organizations in the past 5 years: Aerocrine; AKL Ltd.; Almirall; AstraZeneca; British Lung Foundation; Boehringer Ingelheim; Chiesi; GlaxoSmithKline; Mylan; Mundipharma; Napp; Novartis; Orion; Respiratory Effectiveness Group; Takeda; Teva; and Zentiva, a Sanofi company.

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RJ has received grants from AstraZeneca and GSK, and personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Nutricia and Pfizer outside the submitted work. He was supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South West Peninsula (NIHR CLAHRC South West Peninsula).

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1 **Association between blood eosinophil count and risk of**
2 **readmission for patients with asthma: historical cohort**
3 **study**

4 **Short title:** Blood eosinophil count and risk of readmission for asthma

5

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22

23 **Abstract**

24 **Background**

25 Recent studies have demonstrated an association between high blood eosinophil counts and
26 greater risk of asthma exacerbations. We sought to determine whether patients hospitalized for
27 an asthma exacerbation were at greater risk of readmission if they had a high blood eosinophil
28 count documented before the first hospitalization.

29 **Methods**

30 This historical cohort study drew on 2 years of medical record data (Clinical Practice Research
31 Datalink with Hospital Episode Statistics linkage) of patients (aged ≥ 5 years) admitted to
32 hospital in England for asthma, with recorded blood eosinophil count within 1 baseline year
33 before admission. We analyzed the association between high blood eosinophil count ($\geq 0.35 \times 10^9$
34 cells/L) and readmission risk during 1 year of follow-up after hospital discharge, with adjustment
35 for predefined, relevant confounders using forward selection.

36 **Results**

37 We identified 2,613 eligible patients with asthma-related admission, of median age 51 years
38 (interquartile range, 36-69) and 76% women (1,997/2,613). Overall, 835/2,613 (32.0%) had a
39 preadmission high blood eosinophil count. During the follow-up year, 130/2,613 patients (5.0%)
40 were readmitted for asthma, including 55/835 (6.6%) with vs. 75/1,778 (4.2%) without high
41 blood eosinophil count at baseline (adjusted hazard ratio [HR] 1.49; 95% CI 1.04-2.13, $p=0.029$).
42 The association was strongest in never-smokers ($n=1,296$; HR 2.16, 95% CI 1.27-3.68, $p=0.005$)
43 and absent in current smokers ($n=547$; HR 1.00, 95% CI 0.49-2.04, $p=0.997$).

44 **Conclusions**

45 A high blood eosinophil count in the year before an asthma-related hospitalization is associated with
46 increased risk of readmission within the following year. These findings suggest that patients with asthma
47 and preadmission high blood eosinophil count require careful follow-up, with treatment optimization,
48 after discharge.

49

50 Key words: asthma; eosinophils; patient readmission

51 **Introduction**

52 Severe asthma exacerbations may result in hospital admissions, relatively rare but
53 important events with adverse implications for patients' quality of life, health care resource use,
54 and related costs. Approximately 83,000 hospital episodes (including inpatient, day-case, and
55 intensive care episodes) were recorded as related to asthma in England in 2011-2012,
56 representing approximately 3.3 million patients with clinician-reported, diagnosed-and-treated
57 asthma in England during that time [1].

58 Recent studies have demonstrated an association between high blood eosinophil counts
59 and greater risk of asthma exacerbations, especially in patients with asthma that is not well-
60 controlled [2,3]. Moreover, among patients with severe asthma in a US cohort study, the odds of
61 asthma-related hospital admissions were significantly greater for patients with high blood
62 eosinophil count defined as $\geq 0.4 \times 10^9$ cells/L than for those with counts of $< 0.4 \times 10^9$ cells/L [4].
63 Similarly, in the UK, patients with severe uncontrolled eosinophilic asthma (blood eosinophil
64 count $\geq 0.3 \times 10^9$ cells/L) experienced over 7 times the number of hospitalizations per year
65 compared with the general asthma population [5], and in Finland, a blood eosinophil count
66 $> 0.3 \times 10^9$ cells/L was associated with 13% greater rate of hospital admissions (vs. $\leq 0.3 \times 10^9$
67 cells/L) among patients with asthma [6]. Targeted therapy for patients with severe eosinophilic
68 asthma can reduce the rate of exacerbations requiring hospitalization and/or an emergency
69 department (ED) visit [7,8].

70 Patients who are admitted to hospital for asthma-related reasons, such as a severe
71 exacerbation, may be at risk of short-term readmission to hospital. For example, some patients
72 with persistent airways inflammation are at risk of readmission after discharge despite treatment
73 with corticosteroids [9,10]. Predictors of readmission are important to identify as this

74 information could be used to improve in-hospital and post-hospitalization patient management to
75 minimize subsequent readmissions. Several demographic and socioeconomic risk factors for
76 hospital readmissions have been reported for patients with asthma, including older age, greater
77 number of comorbidities, an urban hospital setting, and longer length of hospital stay [11,12]. A
78 recent study found that elevated blood eosinophil count ($\geq 0.3 \times 10^9$ cells/L) in the first blood
79 sample upon hospitalization was associated with a lower incidence of hospital readmissions as
80 compared with an eosinophil count $< 0.3 \times 10^9$ cells/L [13]. Conversely, for patients with chronic
81 obstructive pulmonary disease (COPD), a recent publication reports an association of increased
82 readmissions with blood eosinophil count $\geq 0.20 \times 10^9$ cells/L at first hospitalization [14]. The
83 variability in associations may be because blood eosinophils are prognostic and theragnostic.

84 The aim of this study was to determine if patients hospitalized for an asthma exacerbation
85 were more likely to be readmitted if their preadmission blood eosinophil count was elevated. Our
86 hypothesis was that standard management of asthma exacerbations is insufficient to prevent
87 readmissions for patients who have high blood eosinophil counts in the year preceding a
88 hospitalization.

89

90 **Methods**

91 **Data source**

92 We used primary and secondary care data from the Clinical Practice Research Datalink
93 (CPRD) and linked Hospital Episode Statistics (HES) for this historical cohort study of patients
94 with asthma who had been admitted to hospital in England. The CPRD is a large well-validated
95 database, frequently used for medical and health research, that contains de-identified,
96 longitudinal medical records of 5 million patients from >600 UK practices [15]. The linked HES

97 data include detailed information about hospital admissions, ED visits, and outpatient visits to
98 secondary care in England [16]. We used the HES Admitted Patient Care database, which
99 contains records of patients who were admitted to a hospital ward, including patients who visited
100 an ED before admission and those who were admitted to an intensive care unit. Diagnostic and
101 treatment data are recorded in the CPRD using Read codes, while diagnosis data are recorded in
102 HES using International Classification of Disease (ICD)-10 clinical coding and OPCS4
103 procedural coding.

104 The study dataset spanned the period from April 1997 through February 2016.

105

106 **Study design and patients**

107 Eligible patients were 5 years or older at the time of their most recent asthma diagnosis
108 and had active asthma, which we defined as (1) a diagnostic Read code for asthma qualifying for
109 inclusion in the asthma registry, which general practices in the UK maintain for the Quality
110 Outcomes Framework (QOF) [17], (2) no recorded asthma-resolved Read code after the last
111 asthma diagnosis code, and (3) at least 2 prescriptions for asthma (controller or reliever
112 medication) during 1 baseline year. Patients admitted to hospital with asthma as the primary
113 diagnosis (ICD-10 code J45-J46) were eligible for the study if they had one or more valid blood
114 eosinophil counts recorded during the year before the hospital admission with no prescription for
115 oral corticosteroids within 2 weeks before the eosinophil count.

116 Eligible patients had to have available, continuous data throughout the study period (Fig
117 1), which included ≥ 1 baseline year before discharge from the hospital for patient
118 characterization and ≥ 1 outcome year after hospital discharge for follow-up (except for patients
119 who died within 1 year after hospital discharge). We included the first hospitalization recorded

120 for each patient meeting those criteria. A diagnostic Read code for any of the following chronic
121 respiratory conditions recorded at any time was cause for exclusion from the study:
122 bronchiectasis, pulmonary sarcoidosis, hypersensitivity pneumonitis, malignancy of the lungs,
123 interstitial lung disease, and cystic fibrosis. Patients with concomitant diagnosis of COPD were
124 not excluded.

125

126 **Fig 1. Study Design.**

127

128 The study was performed in compliance with all applicable local and international laws
129 and regulations and to standards suggested for observational studies, including an independent
130 advisory group, use of an *a priori* analysis plan, and study registration with commitment to
131 publish [18]. The study protocol was approved by the CPRD Independent Scientific Advisory
132 Committee (ISAC approval number 16_236) and registered with the European Union electronic
133 Register of Post-Authorisation Studies (EU PAS Register number EUPAS15869) [19]. No
134 patient identifying information was accessible during the study.

135

136 **Outcome assessments**

137 The exposure of interest was the most recent blood eosinophil count measured within 1
138 year before hospital admission. For patients who had multiple tests in the baseline year, we used
139 the blood eosinophil count (with no oral corticosteroid prescription within 2 weeks prior) that
140 was closest to the admission. A high blood eosinophil count was defined as $\geq 0.35 \times 10^9$ cells/L (or
141 $\geq 0.4 \times 10^9$ cells/L when counts were recorded to only 1 decimal place). This value was chosen
142 based on our findings in a prior study in which patients with blood eosinophil counts $> 0.3 \times 10^9$
143 cells/L experienced more severe exacerbations and poorer asthma control [3].

144 The primary outcome was readmission to hospital with asthma as primary diagnosis
145 (ICD-10 code J45/J46) over a 4-week outcome period and over a 1-year outcome period after
146 discharge from the hospital (Fig 1). The secondary outcome was readmission to hospital with
147 asthma as a secondary/subsidiary diagnosis and a respiratory condition as primary diagnosis
148 (ICD-10 codes J00-J99), again observed over 4 weeks and 1 year.

149

150 **Statistical analysis**

151 Patients' baseline characteristics and hospital readmissions were compared between
152 patients with high and normal blood eosinophil counts using Pearson's χ^2 test of independent
153 categories for categorical variables, and the Mann-Whitney test for continuous variables.

154 Kaplan-Meier curves were constructed for patients with and without high blood
155 eosinophil count for the maximum follow-up period of 1 year after hospital discharge.

156 Comparisons were made with log-rank analyses, and patients were censored if they died.

157 Cox proportional hazard regression, with the time from hospital discharge date to the first
158 readmission date as the "survival" time, was performed to estimate hazard ratios (HRs) with 95%
159 confidence intervals (CIs) for the association between high blood eosinophil count and time to
160 readmission, adjusted for potential confounders. The following variables were evaluated for their
161 potential confounding effect on the effect estimate: sex, age, body mass index (BMI), smoking
162 habits, timing of blood eosinophil count relative to the first hospitalization, Charlson comorbidity
163 index (categorical as 0, 1–4, ≥ 5), comorbidities, and Global Initiative for Asthma [20] (GINA)
164 treatment step (S1 Table). The likelihood of a blood eosinophil count being recorded was greater
165 at dates closer to the hospital admission, and we included the time between recorded eosinophil
166 count and first hospitalization as a confounder in the Cox regression model. Final models were

167 arrived at following a forward-selection procedure, in which variables were added one-by-one
168 and retained if the coefficient for the effect estimate (high eosinophil count) changed by $\geq 5\%$.
169 Co-linearity was checked by evaluating variance inflation factors, which were all under 5%. The
170 validity of the proportional hazards assumption was checked by examination of survival curves,
171 and p-values were calculated using a Wald test.

172 Potential effect modification of smoking status was tested for significance by including
173 an interaction term into the full model. We conducted several sensitivity analyses, repeating the
174 outcome analyses using alternative definitions of high blood eosinophil counts ($\geq 0.25 \times 10^9$
175 cells/L or $\geq 0.3 \times 10^9$ cells/L if rounded, and $\geq 0.45 \times 10^9$ cells/L or $\geq 0.5 \times 10^9$ cells/L if rounded) and
176 examining outcomes in two subsets of patients: (1) after exclusion of those who initiated inhaled
177 corticosteroids (ICS) after their first asthma-related hospital admission and (2) after exclusion of
178 patients with a concomitant diagnosis of COPD.

179 Statistical analyses were conducted using IBM SPSS Statistics version 23 (IBM SPSS
180 Statistics, Feltham, Middlesex, UK) and R version 3.0.2 (The R Project for Statistical
181 Computing; <https://www.r-project.org/>). A statistically significant result was defined as $p \leq 0.05$.

182

183 **Results**

184 **Patients**

185 Of 146,485 patients in the CPRD with HES data linkage, 22,940 (16%) patients had at
186 least one hospital admission for asthma and ≥ 2 years of medical record data, and 3,611 patients
187 (16%) of those hospitalized had an eosinophil count recorded within 1 year before the
188 hospitalization (and no oral corticosteroid prescription within 2 weeks prior). Of these 3,611

189 patients, 2,613 patients (72%) were ≥ 5 years old, had active asthma, and were eligible for the
190 study (Fig 2).

191

192 **Fig 2. Flow Diagram Showing Selection of Eligible Patients from the Database.**

193 CPRD = Clinical Practice Research Database. HES = Hospital Episode Statistics. OCS = oral
194 corticosteroid. QOF = Quality Outcomes Framework.

195

196 In the study population, 482 of 2,613 patients (18%) were discharged from hospital on
197 the same day. Six patients died (one patient died 31 weeks after readmission for asthma and was
198 not censored; others were censored) during 1 year of follow up.

199 Characteristics of the total population with blood eosinophil count ($n=2,613$) and 13,016
200 patients with asthma who met all eligibility criteria except availability of blood eosinophil count
201 during baseline are presented in S2 Table. There were multiple statistically significant
202 differences between the two groups of patients. Eligible patients with recorded eosinophil count
203 were older than the 13,016 patients without eosinophil count (median age, 50 vs. 33 years), more
204 commonly female (1,997/2,613, 76% vs. 7,542/13,016, 58%), heavier (mean BMI 29.1 vs. 26.0
205 kg/m^2), and receiving a higher median ICS dose (219 vs. 132 $\mu\text{g/day}$, fluticasone-propionate
206 equivalent) during the baseline year (S2 Table).

207 A high blood eosinophil count ($\geq 0.35 \times 10^9$ cells/L) was recorded during the year before
208 the hospital admission for 835 of 2,613 patients (32%). The high blood eosinophil cohort had a
209 median age of 45 (vs. 54 years in the cohort with eosinophil count of $< 0.35 \times 10^9$ cells/L) and
210 included proportionately fewer women and fewer overweight and obese patients (Table 1). In
211 addition, patients with eosinophil count $\geq 0.35 \times 10^9$ cells/L were more likely to be never-smokers
212 and to have a recorded diagnosis of rhinitis, atopic eczema, or nasal polyps.

213

214

215 **Table 1. Baseline Demographic and Clinical Characteristics.**

Variable	All patients (N = 2,613)	Blood eosinophil cohort		P value ^a
		<0.35x10 ⁹ cells/L (n = 1,778)	≥0.35x10 ⁹ cells/L (n = 835)	
Age				
Median (IQR)	51.0 (36.0-69.0)	54.0 (39.0-70.3)	45.0 (30.0-65.0)	<0.0001
5-12 years	56 (2.1)	17 (1.0)	39 (4.7)	<0.0001
13-17 years	77 (2.9)	31 (1.7)	46 (5.5)	
18-64 years	1,681 (64.3)	1,141 (64.2)	540 (64.7)	
≥65 years	799 (30.6)	589 (33.1)	210 (25.1)	
Female sex	1,997 (75.7)	1,392 (78.3)	585 (70.1)	<0.0001
Smoking status ^b				
Data available	2,597 (99.4)	1,771 (99.6)	826 (98.9)	
Current smoker	547 (21.1)	378 (21.3)	169 (20.5)	0.007
Ex-smoker	754 (29.0)	544 (30.7)	210 (25.4)	
Never smoker	1,296 (49.9)	849 (47.9)	447 (54.1)	
Body mass index ^b				
Data available	2,260 (86.5)	1,551 (87.2)	709 (84.9)	
Mean (SD)	29.2 (7.0)	29.6 (7.0)	28.4 (7.0)	<0.0001
<18.5 kg/m ²	78 (3.5)	38 (2.5)	40 (5.6)	<0.0001
≥18.5 kg/m ² to <25 kg/m ²	625 (27.7)	393 (25.3)	232 (32.7)	
≥25 kg/m ² to <30 kg/m ²	625 (27.7)	450 (29.0)	175 (24.7)	
≥30 kg/m ²	932 (41.2)	670 (43.2)	262 (37.0)	
Allergic/non-allergic rhinitis ^c	876 (33.5)	545 (30.7)	331 (39.6)	<0.0001
Atopic eczema ^c	927 (35.5)	595 (33.5)	332 (39.8)	<0.0001
Nasal polyps ^c	83 (3.2)	39 (2.2)	44 (5.3)	<0.0001
Chronic rhinosinusitis ^c	579 (22.2)	400 (22.5)	179 (21.4)	0.54
COPD ^c	284 (10.9)	192 (10.8)	92 (11.0)	0.87
GERD ^c	474 (18.1)	355 (20.0)	119 (14.3)	<0.001
Cardiovascular disease ^c	654 (25.0)	491 (27.6)	163 (19.5)	<0.0001
Charlson comorbidity index				
0	611 (23.4)	429 (24.1)	182 (21.8)	0.028
1-4	1,661 (63.6)	1,101 (61.9)	560 (67.1)	
≥5	341 (13.1)	248 (13.9)	93 (11.1)	
GINA step of asthma treatment ^b				
1	124 (4.7)	78 (4.4)	46 (5.5)	0.009
2	493 (18.9)	357 (20.1)	136 (16.3)	
3	468 (17.9)	298 (16.8)	170 (20.4)	
4	1,220 (46.7)	848 (47.7)	372 (44.6)	
5	308 (11.8)	197 (11.1)	111 (13.3)	
≥1 ICS inhaler prescribed	2,444 (93.5)	1,671 (94.0)	773 (92.6)	0.173

Daily dose of ICS ($\mu\text{g}/\text{day}$), median (IQR) ^d	262 (110-521)	263 (110-534)	247 (99-492)	0.041
≥ 1 SABA inhaler prescribed	2,432 (93.1)	1,646 (92.6)	786 (94.1)	0.144
Daily SABA dose, median (IQR) ^d	1.64 (0.82-3.55)	1.64 (0.66-3.29)	2.04 (0.82-4.11)	<0.0001
OCS daily dose (g), median (IQR)	0.55 (0-1.64)	0.55 (0-1.56)	0.55 (0-1.75)	0.139
No. severe asthma exacerbations				
0	747 (28.6)	516 (29.0)	231 (27.7)	0.25
1	848 (32.5)	589 (33.1)	259 (31.0)	
2	506 (19.4)	345 (19.4)	161 (19.3)	
3	266 (10.2)	174 (9.8)	92 (11.0)	
≥ 4	246 (9.4)	154 (8.7)	92 (11.0)	

216 Data expressed as No. (%) unless otherwise noted. COPD = chronic obstructive pulmonary disease. GERD =
 217 gastroesophageal reflux disease. GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; OCS = oral
 218 corticosteroid; SABA = short-acting β -agonist.

219 ^aP-value comparing blood eosinophil cohorts, computed from χ^2 test for categorical variables, or Mann-Whitney test,
 220 for continuous variables. Where variables are presented as both continuous and categorical, the p-value is from the
 221 Mann-Whitney test.

222 ^bThe closest BMI within 10 years of hospital discharge, and the smoking status closest to and within 5 years before
 223 hospital discharge, were included. The GINA treatment step was determined based on the last prescription before
 224 the hospitalization (S1 Table). The BMI categories applied to patients ≥ 18 years old; for children, BMI was not
 225 calculated because accurate information on age in months required to calculate BMI z-scores was not provided for
 226 privacy reasons.

227 ^cComorbidities were those with diagnostic Read code ever-recorded in the available data before hospital discharge.

228 ^dICS dose expressed as fluticasone propionate equivalent ($\mu\text{g}/\text{day}$), and one SABA dose defined as 200 μg in
 229 albuterol equivalents.

230

231

232 The likelihood of a blood eosinophil count being recorded was greater at dates closer to
 233 the hospital admission (S1 Fig). Patients with measurements within 4 weeks before the
 234 hospitalization were more likely to have a high blood eosinophil count (128/339, 38%) than
 235 those with measurement within a longer time period before the hospitalization (707/2274, 31%;
 236 $p=0.014$). The length of time between recorded eosinophil count and admission with asthma as
 237 the primary diagnosis was greater in patients with high blood eosinophil counts than in patients
 238 without high counts, but the difference in distribution was not statistically significant (144 days
 239 [IQR, 56–250] vs. 131 days [58–229], $p=0.159$).

240 The median duration of hospitalization (2 nights) was the same in patients with and
 241 without a high blood eosinophil count; however, there were fewer patients with a high blood
 242 eosinophil count who had a long hospital stay (Table 2).

243

244 **Table 2. Duration of Hospitalization.**

Variable	All patients (N = 2,613)	Blood eosinophil cohort		P value ^a
		<0.35x10 ⁹ cells/L (n = 1,778)	≥0.35x10 ⁹ cells/L (n = 835)	
Nights in hospital, median (IQR)		2 (1–5)	2 (1–4)	
No. nights in hospital, n (%)				
0	482 (18.4)	323 (18.2)	159 (19.0)	0.006
1	529 (20.2)	349 (19.6)	180 (21.6)	
2	356 (13.6)	230 (12.9)	126 (15.1)	
3	281 (10.8)	182 (10.2)	99 (11.9)	
4	243 (9.3)	162 (9.1)	81 (9.7)	
5	149 (5.7)	99 (5.6)	50 (6.0)	
6	142 (5.4)	106 (6.0)	36 (4.3)	
≥7	431 (16.5)	327 (18.4)	104 (12.5)	

245 ^aP-value comparing blood eosinophil cohorts computed from χ^2 test.

246

247 Readmissions by eosinophil cohort

248 Only 6 patients were readmitted to the hospital within 4 weeks of the first admission,
 249 with no significant difference between blood eosinophil cohorts (Table 3). At 1 year, 130 of
 250 2,613 (5%) patients overall were readmitted for asthma, including a significantly greater
 251 percentage of patients with high vs. normal blood eosinophil count (Table 3; Fig 3). Patients with
 252 eosinophil count of $\geq 0.35 \times 10^9$ cells/L had a 49% higher adjusted risk of readmission to hospital
 253 for asthma in the first year of follow-up than patients without a high count (HR 1.49; 95% CI
 254 1.04–2.13; p=0.029; Table 3).

255

256 **Table 3. Readmissions to Hospital within 4 Weeks and 1 Year and Hazard Ratios for**
 257 **Readmission in the High Eosinophil Count Cohort.**

Readmission	Eosinophil cohort		P value ^a	Adjusted HR (95% CI) for blood eosinophil count $\geq 0.35 \times 10^9/L^b$	P value
	<0.35x10 ⁹ cells/L (n = 1,778)	$\geq 0.35 \times 10^9$ cells/L (n = 835)			
With asthma as primary diagnosis (n = 2,613)					
Within 4 weeks	4 (0.2)	2 (0.2)	0.94	--	--
Within 1 year	75 (4.2)	55 (6.6)	0.009	1.49 (1.04-2.13)	0.029
By known smoking status (n = 2,597) ^c					
Never-smokers (n = 1,296)	29 (3.4)	30 (6.7)	0.007	2.16 (1.27-3.68)	0.005
Ex-smokers (n = 754)	19 (3.5)	13 (6.2)	0.010	1.49 (0.73-3.06)	0.27
Current smokers (n = 547)	27 (7.1)	12 (7.1)	0.99	1.00 (0.49-2.04)	0.997
Never/ex-smokers pooled (n = 2,050)	48 (3.4)	43 (6.5)	0.002	1.78 (1.17-2.73)	0.007
With respiratory condition other than asthma, and asthma as subsidiary diagnosis (n = 2,613)					
Within 4 weeks	22 (1.2)	8 (1.0)	0.53	--	--
Within 1 year	81 (4.6)	39 (4.7)	0.90	1.12 (0.76-1.65)	0.57

258 ^aP-value computed using χ^2 test.

259 ^bAdjusted for sex, age, smoking status, timing of blood eosinophil count measurement, duration of index
 260 hospitalization.

261 ^c16 patients with no recent record of smoking status were excluded from the analyses by smoking status.

262
 263

264 **Fig 3. Kaplan-Meier Curves Describing the Cumulative “Survival” of a Readmission to**
 265 **Hospital for Asthma in the First Year After an Admission with Asthma as the Primary**
 266 **Diagnosis in Patients With and Without High Blood Eosinophil Count.**

267

268 **Interaction with smoking status**

269 The effect of current smoking was non-significant ($p=0.073$) when tested by including an
270 interaction term for current smoking (yes/no) and high blood eosinophil count (yes/no) into the
271 model. The increased readmission rate with a high blood eosinophil count was found only in
272 non-smokers (HR 1.84; 1.20–2.80; $p=0.005$) and not in current smokers (HR 0.88; 0.44–1.76;
273 $p=0.73$). In this analysis of all 2,613 patients, 16 patients without recent, recorded smoking status
274 were included as non-smokers (never-smokers plus ex-smokers).

275 Results were similar for patients with known smoking status, with a significant 216%
276 higher adjusted risk of readmission for never-smokers with high blood eosinophil count, and no
277 additional risk for current smokers with high blood eosinophil count (Table 3). Although the
278 association was most pronounced in never-smokers, no significant difference in the association
279 was found between never-smokers and ex-smokers ($p=0.67$) in the 2,050 patients recorded as not
280 currently smoking.

281

282 **Sensitivity analyses**

283 A high blood eosinophil count was recorded for 1,328 patients (51%) when defined as
284 $\geq 0.25 \times 10^9$ cells/L, and for 588 patients (23%) when defined as $\geq 0.45 \times 10^9$ cells/L. The
285 association between a high blood eosinophil count and readmission to hospital for asthma was
286 less pronounced and not significant for patients with blood eosinophil count of either $\geq 0.25 \times 10^9$
287 cells/L (HR=1.17; 0.82–1.66; $p=0.39$) or $\geq 0.45 \times 10^9$ cells/L (HR=1.15; 0.77–1.72; $p=0.50$; S3
288 Table). The association was also not significant in never-smokers or in never/ex-smokers
289 combined using either definition of high blood eosinophil count (S3 Table).

290 A total of 169 of the 2,613 patients (6%) had no prescription for ICS in the baseline year
291 before being hospitalized for asthma; of the 169, 115 (68%) had ICS prescribed in the outcome

292 year. After exclusion of these 115 patients, HRs for the association with blood eosinophil count
293 of $\geq 0.35 \times 10^9$ cells/L slightly increased as compared with those for the full population (S3 Table).
294 The HR was 1.77 (95% CI, 1.15–2.72; $p=0.009$) for never/ex-smokers combined, which was
295 very similar to the HR for never/ex-smokers combined of the full population (1.78). However,
296 effect modification by current smokers was not significant in this subpopulation ($p=0.28$).

297 Results of an additional subanalysis excluding patients with a concomitant diagnosis of
298 COPD showed no relevant difference in association for the remaining 2,329 patients (HR= 1.48;
299 95% CI 1.01–2.17, $p=0.045$; see S3 Table).

300

301 Discussion

302 In this large, historical cohort study, we found that patients who had a blood eosinophil
303 count of $\geq 0.35 \times 10^9$ cells/L recorded in the year preceding an asthma-related hospitalization had a
304 significantly greater risk of readmission for asthma during the year after they were discharged.
305 Few patients ($n=6$) were readmitted to hospital for asthma within 4 weeks after discharge, while
306 by 1 year after discharge, 5% (130 of 2,613) patients were readmitted for asthma. The greater
307 risk of readmission during 1 year follow-up was present only for patients with high blood
308 eosinophil count who were never- or ex-smokers (not for current smokers).

309 Our study is one of few studies examining hospital readmissions for asthma in a general
310 asthma population and in the real-life setting. Readmissions in the present study were
311 comparatively infrequent relative to results in other studies: for example, in one US study,
312 approximately 4% of patients were readmitted for an asthma exacerbation within 30 days [21],
313 and in France from 2002–2005, 15% were readmitted for asthma within 1 year [22]. The overall

314 rate of hospital admissions for asthma in England appears to be lower than for Western
315 Europe as a whole, the latter reported in 2004 to be 7% [1,23].

316 Other recent studies of hospital readmissions have been limited to patients on systemic
317 corticosteroids [9], have examined readmissions up to only 30 days [11,12,24], were much
318 smaller [24], and/or were conducted at a single institution [25,26]. None of these studies, nor
319 others examining readmissions after 30 days [27-29], examined the association of hospital
320 readmissions with blood eosinophil count. While Gonzalez-Barcala et al. [13] in their
321 retrospective study at a single hospital in Spain found differently from the present study that
322 elevated eosinophil count was associated with a lower incidence of readmissions, it is difficult to
323 compare their study with ours because of differences in methods. For example, the reference
324 blood eosinophil count was that taken upon admission rather than before hospitalization during a
325 baseline year, and the length of the follow-up period for analyzing readmissions is unclear [13].

326 An interesting finding in the present study that requires further investigation is the effect
327 of smoking status on association of readmissions with eosinophil count. Cigarette smoking
328 increases levels of oxidative stress, alters airway immune responses, and increases risk of
329 hospitalization in patients with asthma [30]. Westerhof et al. [31] in their study of patients with
330 severe asthma found that frequent exacerbations were associated with blood eosinophil count
331 only in never smokers and not in ex-smokers, for whom blood neutrophil count was an
332 independent predictor of frequent exacerbations (smokers not studied). In our study, both never-
333 and ex-smokers (but not current smokers) who had a high eosinophil count were at greater risk of
334 asthma-related readmission, although for ex-smokers separately this association was not
335 statistically significant. Moreover, in our study the difference in association between non-
336 smokers (never-plus ex-smokers pooled) and smokers was large and statistically significant.

337 Clearly, additional work is needed to examine biomarker and peripheral blood cell profiles in
338 relation to smoking status and hospital readmissions and other asthma-related outcomes.

339 The median duration of hospitalization (2 nights) was the same in both normal and high
340 blood eosinophil cohorts; however, patients with a high blood eosinophil count were less likely
341 to have a hospital stay longer than 5 nights (17% vs. 24% of those without high eosinophil
342 count). This finding illustrates the conundrum of eosinophilic asthma: while it tends to be more
343 severe in terms of exacerbations and asthma control, eosinophilic asthma is also potentially more
344 responsive to therapies targeting type 2 inflammation, including ICS and biologics.

345 We speculated that the association between eosinophil count and readmission could be
346 diluted for patients with eosinophil count performed several months before the first admission;
347 therefore, we re-examined outcomes including only patients with eosinophil counts measured
348 close to the initial hospitalization to see if the association were stronger. However, when
349 selecting those with eosinophil count recorded within 4 months before hospitalization, the
350 numbers became small and associations non-significant, although the direction of the effect was
351 the same: for never- and ex-smokers pooled (n=915), the risk of readmission was 51% greater
352 but non-significant (adjusted HR 1.69;0.60–4.76; p=0.32).

353 A strength of this study is that we included a broad patient population with asthma, not
354 limited to those with severe asthma. We selected inclusion criteria to ensure that patients' asthma
355 was actively managed in advance of the hospital admission, thereby excluding patients
356 experiencing a first episode of asthma diagnosed at the time of admission. Moreover, we
357 required that patients had not received an oral corticosteroid prescription within 2 weeks before
358 the eosinophil count to obviate the eosinopenic effects of systemic corticosteroids [32,33]. The
359 data sources we used are well-regarded and frequently employed for pharmacoepidemiological

360 studies [15-17,34]. The primary care data in the CPRD is considered to be high-quality, with
361 recording that has been standardized and improved since the institution in 2004 of the UK
362 Quality Outcomes Framework (QOF) [17], which provides financial incentives for GPs to
363 deliver quality care, including an annual asthma review covering asthma control status, smoking,
364 and inhaler technique. Detailed information about hospital admissions was drawn from HES, a
365 data warehouse linked to the CPRD [16].

366 Nevertheless, a limitation is that the study dataset comprised information collected for
367 clinical and routine use rather than specifically for research purposes. Moreover, prescriptions
368 for drugs prescribed by specialists are not reliably recorded in the CPRD. Therefore, we could
369 not evaluate treatment prescribed immediately after hospital discharge. However, the daily dose
370 of ICS prescribed by GPs in the year after admission was not significantly different between
371 patients with and without high eosinophil counts (median for both: 329 vs. 329 $\mu\text{g}/\text{day}$
372 fluticasone-equivalent, $p=0.70$, Mann-Whitney test). Finally, as for all observational studies,
373 there is the possibility of residual confounding from unrecognized and/or unmeasured factors.

374 A “count-response” association of blood eosinophil levels with risk of asthma
375 exacerbations has been reported in both an observational study [3] and for the placebo arm of
376 clinical trials [35,36]. Our study had insufficient patient numbers to assess the presence of a
377 count-response relationship with hospital readmissions using incremental categories to define
378 high eosinophil count. Our definition of $\geq 0.35 \times 10^9$ cells/L for high blood eosinophil count
379 captured a clear association of high blood eosinophil count with risk of readmission, while there
380 were fewer patients, hence limited statistical power, to evaluate the higher cut-point of $\geq 0.45 \times 10^9$
381 cells/L, although the direction of the effect was the same. Alternatively, new ICS use or better
382 ICS adherence after the index hospitalization might have reduced the effect of elevated

383 eosinophil count; however, it would not be easy to quantify this possibility in the framework of a
384 historical cohort study, and in spite of this possibility we found a strong association at the
385 $\geq 0.35 \times 10^9$ cells/L definition.

386 We did not exclude patients with a concomitant diagnosis of COPD; therefore,
387 approximately one-tenth of the study population appeared to have some form of physician-
388 diagnosed asthma-COPD overlap [37], although these patients were too few to analyze
389 separately. However, the sensitivity analysis excluding these patients supported the findings for
390 the full population.

391 By necessity we were able to include only patients who had a recorded blood eosinophil
392 count, which is not routinely measured in clinical practice, a factor serving as a possible source
393 of selection bias and thereby limiting the generalizability of our findings. There were large
394 differences in baseline characteristics between the patients with available eosinophil count and
395 those without, who tended to be younger; more likely female, a current smoker, and of normal
396 weight; and less likely having comorbidities such as rhinitis, chronic sinusitis, gastroesophageal
397 reflux disease, and cardiovascular disease. The age differences were expected because older
398 people more frequently have full blood counts available. Further work is needed to examine the
399 use of blood eosinophil count in the clinical assessment of the full spectrum of patients with
400 asthma.

401 Tailoring asthma therapy using sputum eosinophil counts appears to be effective in
402 reducing exacerbations, particularly for adults with frequent exacerbations [38]. Thus, blood
403 eosinophil count, more practical to measure than sputum eosinophil count, could play a role in
404 tailoring asthma therapy with the goal of reducing exacerbations, hence potentially hospital
405 readmissions. Moreover, further research is needed to identify the mechanism(s) behind the

406 increased risk of readmission associated with high blood eosinophil count, such as possible
407 undertreatment with ICS or insufficient effectiveness of ICS. In addition, more specifically, a re-
408 examination is needed of the absence of association with readmissions and high blood eosinophil
409 count in current smokers, as there was limited statistical power in this subgroup of patients,
410 reflected by the wide confidence interval.

411

412 **Conclusions**

413 A high blood eosinophil count in the year before an asthma-related hospitalization is
414 associated with increased risk of readmission within the following year. This risk was slightly
415 greater in the subset of patients who were not new initiators of ICS treatment after their index
416 hospital admission, suggesting that this trait is only partially treatable with anti-inflammatory
417 therapy. This association was present only in non-smoking patients with high blood eosinophil
418 count. Our findings support the benefit of including a full blood count with differential as a
419 routine assessment in clinical practice for patients with not well-controlled asthma. Moreover,
420 our findings support the need for careful follow-up, with treatment optimization, after hospital
421 discharge for patients with asthma and preadmission high blood eosinophil count.

422

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426

427

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547 **Supporting information**

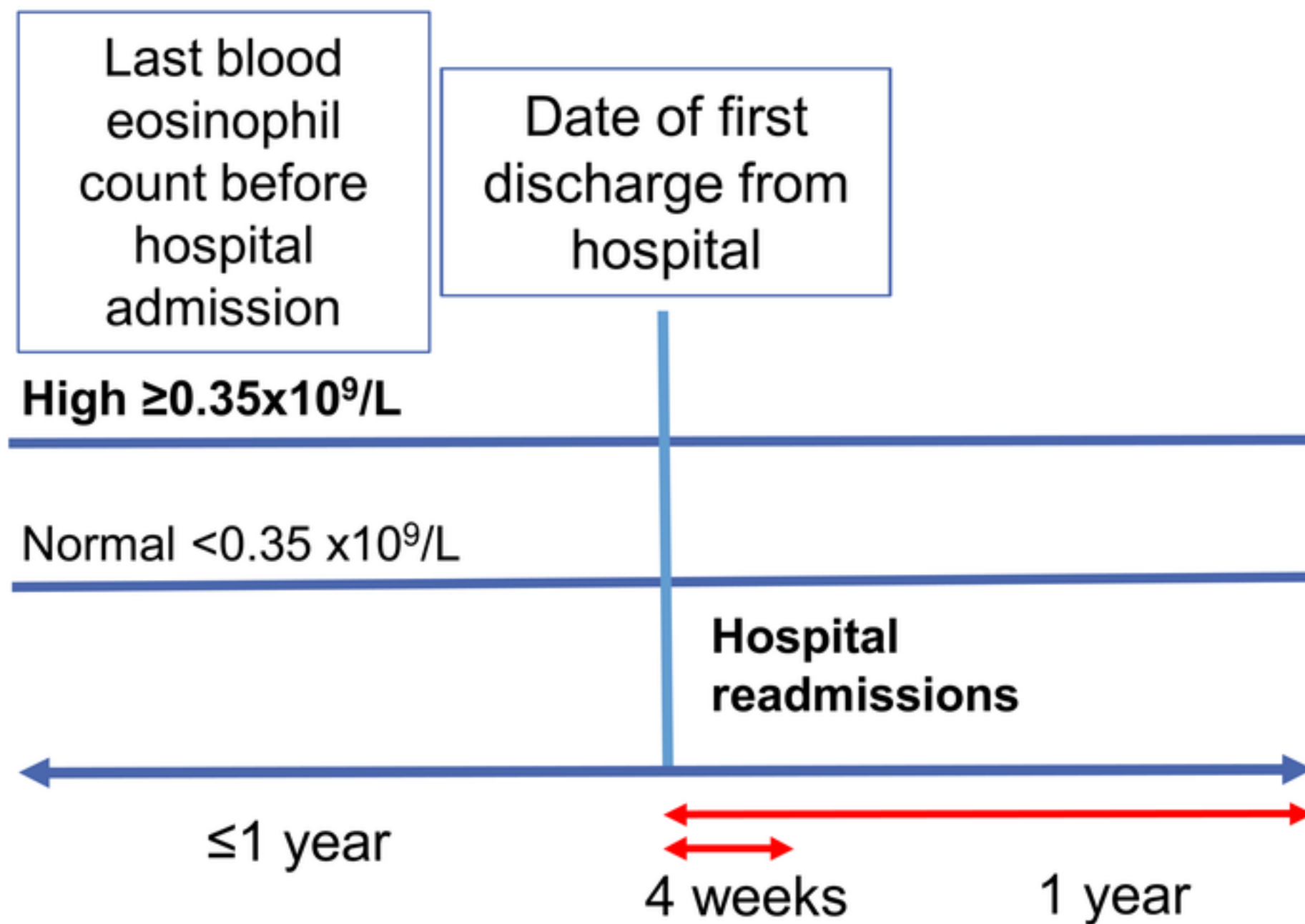
548 **S1 Table. Definitions Applied for Global Initiative for Asthma (GINA) Treatment Step,**
549 **Determined Using Each Patient’s Last Prescription(s) Before the First Hospital Admission.**

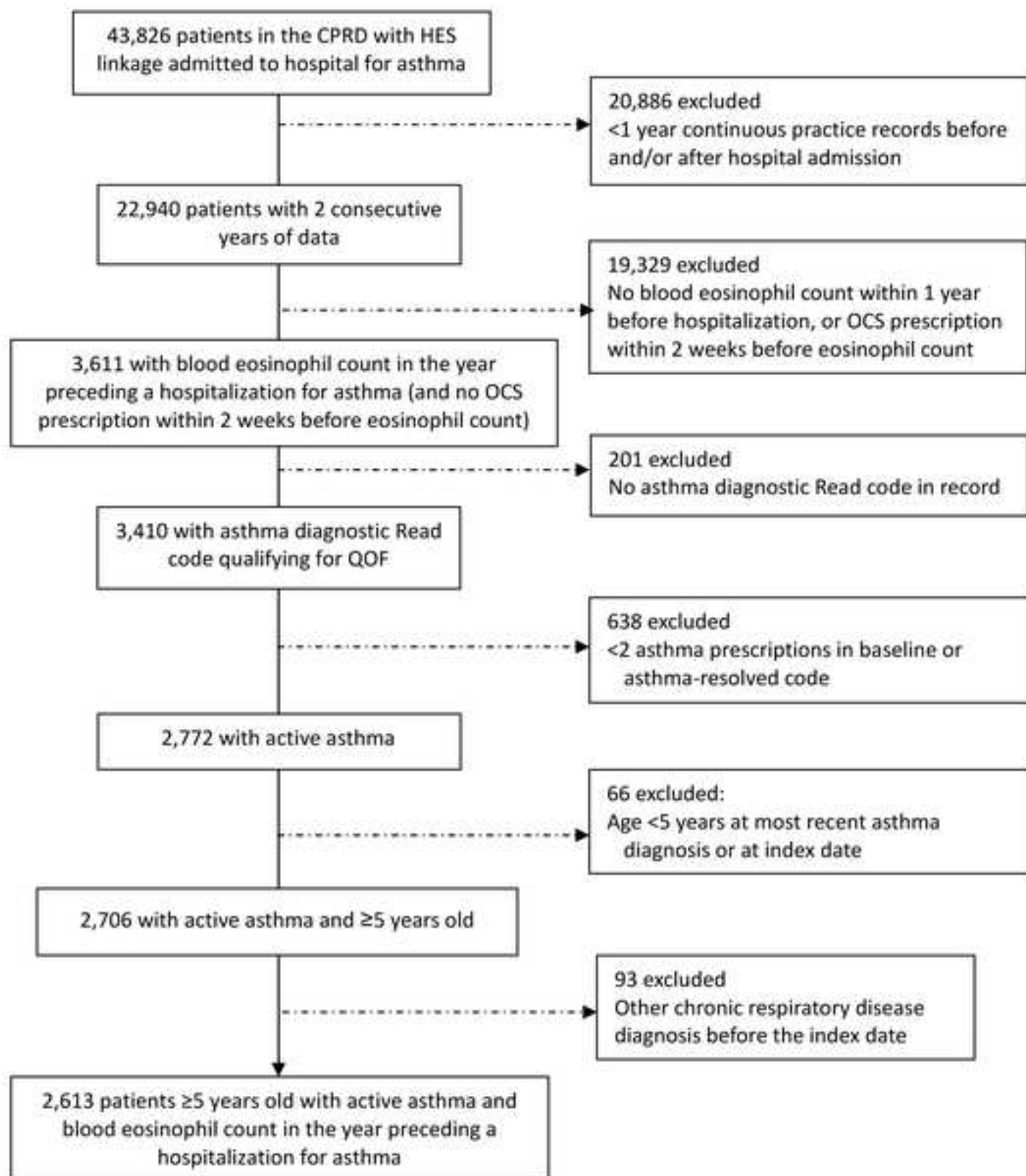
550 **S2 Table. Demographic and Clinical Characteristics of All Eligible Patients with Blood**
551 **Eosinophil Count and of Patients Meeting All Eligibility Criteria Except Availability of**
552 **Eosinophil Count.^a**

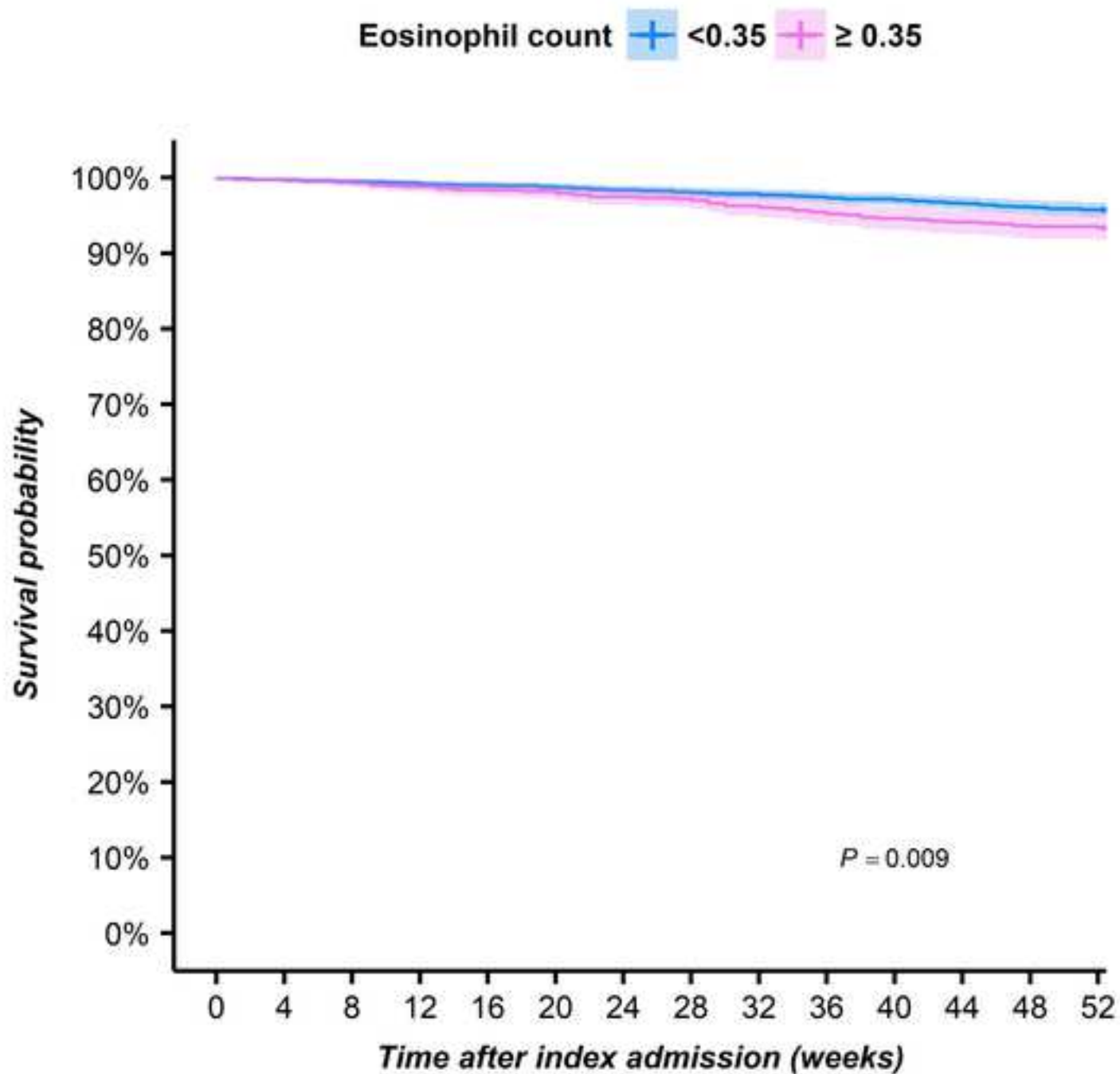
553 **S1 Fig. Distribution of the Number of Days before Hospital Discharge on Which the Most**
554 **Recent Eosinophil Measurement Was Recorded.**

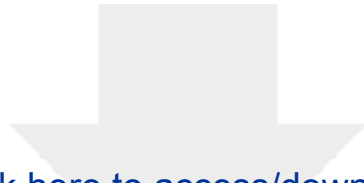
555 **S3 Table. Readmissions for Asthma within 1 Year and Hazard Ratios for Readmission in**
556 **the High Eosinophil Count Cohort: Sensitivity Analyses.**

557





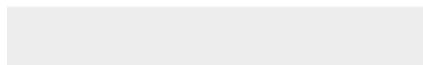


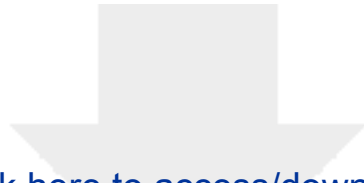


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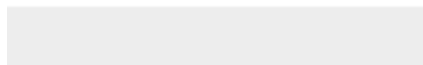




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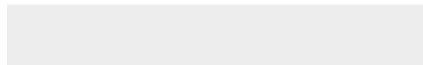
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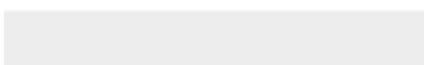

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Revised S3 Table with Track Changes (PONE-D-18-12337).docx

1 **Association between blood eosinophil count and risk of**
2 **readmission for patients with asthma: historical cohort**
3 **study**

4 **Short title:** Blood eosinophil count and risk of readmission for asthma

5

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22

23 **Abstract**

24 **Background**

25 Recent studies have demonstrated an association between high blood eosinophil counts and
26 greater risk of asthma exacerbations. We sought to determine whether patients hospitalized for
27 an asthma exacerbation were at greater risk of readmission if they had a high blood eosinophil
28 count documented before the first hospitalization.

29 **Methods**

30 This historical cohort study drew on 2 years of medical record data (Clinical Practice Research
31 Datalink with Hospital Episode Statistics linkage) of patients (aged ≥ 5 years) admitted to
32 hospital in England for asthma, with recorded blood eosinophil count within 1 baseline year
33 before admission. We analyzed the association between high blood eosinophil count ($\geq 0.35 \times 10^9$
34 cells/L) and readmission risk during 1 year of follow-up after hospital discharge, with adjustment
35 for predefined, relevant confounders using forward selection.

36 **Results**

37 We identified 2,613 eligible patients with asthma-related admission, of median age 51 years
38 (interquartile range, 36-69) and 76% women (1,997/2,613). Overall, 835/2,613 (32.0%) had a
39 preadmission high blood eosinophil count. During the follow-up year, 130/2,613 patients (5.0%)
40 were readmitted for asthma, including 55/835 (6.6%) with vs. 75/1,778 (4.2%) without high
41 blood eosinophil count at baseline (adjusted hazard ratio [HR] [1.451.49](#); 95% CI [1.0204-2.0813](#),
42 $p=0.040029$). The association was strongest in never-smokers ($n=1,296$; HR [1.952.16](#), 95% CI
43 [1.161.27-3.313.68](#), $p=0.013005$) and absent in current smokers ($n=547$; HR [0.971.00](#), 95% CI
44 [0.4849-1.972.04](#), $p=0.94997$).

45 **Conclusions**

46 A high blood eosinophil count in the year before an asthma-related hospitalization is associated with
47 increased risk of readmission within the following year. These findings suggest that patients with asthma
48 and preadmission high blood eosinophil count require careful follow-up, with treatment optimization,
49 after discharge.

50

51 Key words: asthma; eosinophils; patient readmission

52 **Introduction**

53 Severe asthma exacerbations may result in hospital admissions, relatively rare but
54 important events with adverse implications for patients' quality of life, health care resource use,
55 and related costs. Approximately 83,000 hospital episodes (including inpatient, day-case, and
56 intensive care episodes) were recorded as related to asthma in England in 2011-2012,
57 representing approximately 3.3 million patients with clinician-reported, diagnosed-and-treated
58 asthma in England during that time [1].

59 Recent studies have demonstrated an association between high blood eosinophil counts
60 and greater risk of asthma exacerbations, especially in patients with asthma that is not well-
61 controlled [2,3]. Moreover, among patients with severe asthma in a US cohort study, the odds of
62 asthma-related hospital admissions were significantly greater for patients with high blood
63 eosinophil count defined as $\geq 0.4 \times 10^9$ cells/L than for those with counts of $< 0.4 \times 10^9$ cells/L [4].
64 Similarly, in the UK, patients with severe uncontrolled eosinophilic asthma (blood eosinophil
65 count $\geq 0.3 \times 10^9$ cells/L) experienced over 7 times the number of hospitalizations per year
66 compared with the general asthma population [5], and in Finland, a blood eosinophil count
67 $> 0.3 \times 10^9$ cells/L was associated with 13% greater rate of hospital admissions (vs. $\leq 0.3 \times 10^9$
68 cells/L) among patients with asthma [6]. Targeted therapy for patients with severe eosinophilic
69 asthma can reduce the rate of exacerbations requiring hospitalization and/or an emergency
70 department (ED) visit [6,7,8].

71 Patients who are admitted to hospital for asthma-related reasons, such as a severe
72 exacerbation, may be at risk of short-term readmission to hospital. For example, some patients
73 with persistent airways inflammation are at risk of readmission after discharge despite treatment
74 with corticosteroids [8,9,10]. Predictors of readmission are important to identify as this

75 information could be used to improve in-hospital and post-hospitalization patient management to
76 minimize subsequent readmissions. ~~While s~~Several demographic and socioeconomic risk factors
77 for hospital readmissions have been reported for patients with asthma, including older age,
78 greater number of comorbidities, an urban hospital setting, and longer length of hospital stay
79 [10,11,12]. A recent study found that, the association between elevated blood eosinophil count
80 and ($\geq 0.3 \times 10^9$ cells/L) in the first blood sample upon hospitalization was associated with a lower
81 incidence of hospital readmissions as compared with an eosinophil count $< 0.3 \times 10^9$ cells/L
82 [13]. has not been examined for a general asthma population. For Conversely, for patients with
83 chronic obstructive pulmonary disease (COPD), a recent publication reports an association of
84 increased readmissions with blood eosinophil count $\geq 0.20 \times 10^9$ cells/L at first hospitalization
85 [12,14]. The variability in associations may be because blood eosinophils are prognostic and
86 theragnostic.

87 The aim of this study was to determine if patients hospitalized for an asthma exacerbation
88 were more likely to be readmitted if their preadmission blood eosinophil count was elevated. Our
89 hypothesis was that standard management of asthma exacerbations is insufficient to prevent
90 readmissions for patients who have high blood eosinophil counts in the year preceding a
91 hospitalization.

92

93 **Methods**

94 **Data source**

95 We used primary and secondary care data from the Clinical Practice Research Datalink
96 (CPRD) and linked Hospital Episode Statistics (HES) for this historical cohort study of patients
97 with asthma who had been admitted to hospital in England. The CPRD is a large well-validated

98 database, frequently used for medical and health research, that contains de-identified,
99 longitudinal medical records of 5 million patients from >600 UK practices [1315]. The linked
100 HES data include detailed information about hospital admissions, ED visits, and outpatient visits
101 to secondary care in England [1416]. We used the HES Admitted Patient Care database, which
102 contains records of patients who were admitted to a hospital ward, including patients who visited
103 an ED before admission and those who were admitted to an intensive care unit. Diagnostic and
104 treatment data are recorded in the CPRD using Read codes, while diagnosis data are recorded in
105 HES using International Classification of Disease (ICD)-10 clinical coding and OPCS4
106 procedural coding.

107 The study dataset spanned the period from April 1997 through February 2016.

108

109 **Study design and patients**

110 Eligible patients were 5 years or older at the time of their most recent asthma diagnosis
111 and had active asthma, which we defined as (1) a diagnostic Read code for asthma qualifying for
112 inclusion in the asthma registry, which general practices in the UK maintain for the Quality
113 Outcomes Framework (QOF) [1517], (2) no recorded asthma-resolved Read code after the last
114 asthma diagnosis code, and (3) at least 2 prescriptions for asthma (controller or reliever
115 medication) during 1 baseline year. Patients admitted to hospital with asthma as the primary
116 diagnosis (ICD-10 code J45-J46) were eligible for the study if they had one or more valid blood
117 eosinophil counts recorded during the year before the hospital admission with no prescription for
118 oral corticosteroids within 2 weeks before the eosinophil count.

119 Eligible patients had to have available, continuous data throughout the study period (Fig
120 1), which included ≥ 1 baseline year before discharge from the hospital for patient

121 characterization and ≥ 1 outcome year after hospital discharge for follow-up (except for patients
122 who died within 1 year after hospital discharge). We included the first hospitalization recorded
123 for each patient meeting those criteria. A diagnostic Read code for any of the following chronic
124 respiratory conditions recorded at any time was cause for exclusion from the study:
125 bronchiectasis, pulmonary sarcoidosis, hypersensitivity pneumonitis, malignancy of the lungs,
126 interstitial lung disease, and cystic fibrosis. Patients with concomitant diagnosis of COPD were
127 not excluded.

128 129 **Fig 1. Study Design.**

130
131 The study was performed in compliance with all applicable local and international laws
132 and regulations and to standards suggested for observational studies, including an independent
133 advisory group, use of an *a priori* analysis plan, and study registration with commitment to
134 publish [4618]. The study protocol was approved by the CPRD Independent Scientific Advisory
135 Committee (ISAC approval number 16_236) and registered with the European Union electronic
136 Register of Post-Authorisation Studies (EU PAS Register number EUPAS15869) [4719]. No
137 patient identifying information was accessible during the study.

138 139 **Outcome assessments**

140 The exposure of interest was the most recent blood eosinophil count measured within 1
141 year before hospital admission. For patients who had multiple tests in the baseline year, we used
142 the blood eosinophil count (with no oral corticosteroid prescription within 2 weeks prior) that
143 was closest to the admission. A high blood eosinophil count was defined as $\geq 0.35 \times 10^9$ cells/L (or
144 $\geq 0.4 \times 10^9$ cells/L when counts were recorded to only 1 decimal place). This value was chosen

145 based on our findings in a prior study in which patients with blood eosinophil counts $>0.3 \times 10^9$
146 cells/L experienced more severe exacerbations and poorer asthma control [3].

147 The primary outcome was readmission to hospital with asthma as primary diagnosis
148 (ICD-10 code J45/J46) over a 4-week outcome period and over a 1-year outcome period after
149 discharge from the hospital (Fig 1). The secondary outcome was readmission to hospital with
150 asthma as a secondary/subsidiary diagnosis and a respiratory condition as primary diagnosis
151 (ICD-10 codes J00-J99), again observed over 4 weeks and 1 year.

152

153 **Statistical analysis**

154 Patients' baseline characteristics and hospital readmissions were compared between
155 patients with high and normal blood eosinophil counts using Pearson's χ^2 test of independent
156 categories for categorical variables, and the Mann-Whitney test for continuous variables.

157 Kaplan-Meier curves were constructed for patients with and without high blood
158 eosinophil count for the maximum follow-up period of 1 year after hospital discharge.

159 Comparisons were made with log-rank analyses, and patients were censored if they died.

160 Cox proportional hazard regression, with the time from hospital discharge date to the first
161 readmission date as the "survival" time, was performed to estimate hazard ratios (HRs) with 95%
162 confidence intervals (CIs) for the association between high blood eosinophil count and time to
163 readmission, adjusted for potential confounders. The following variables were evaluated for their
164 potential confounding effect on the effect estimate: sex, age, body mass index (BMI), smoking
165 habits, timing of blood eosinophil count relative to the first hospitalization, Charlson comorbidity
166 index (categorical as 0, 1–4, ≥ 5), comorbidities, and Global Initiative for Asthma [1820] (GINA)
167 treatment step (S1 Table). The likelihood of a blood eosinophil count being recorded was greater

168 at dates closer to the hospital admission, and we included the time between recorded eosinophil
169 count and first hospitalization as a confounder in the Cox regression model. Final models were
170 arrived at following a forward-selection procedure, in which variables were added one-by-one
171 and retained if the coefficient for the effect estimate (high eosinophil count) changed by $\geq 5\%$.
172 Co-linearity was checked by evaluating variance inflation factors, which were all under 5%. The
173 validity of the proportional hazards assumption was checked by examination of survival curves,
174 and p-values were calculated using a Wald test.

175 Potential effect modification of smoking status was tested for significance by including
176 an interaction term into the full model. We conducted ~~two~~ several sensitivity analyses, repeating
177 the outcome analyses using alternative definitions of high blood eosinophil counts ($\geq 0.25 \times 10^9$
178 cells/L or $\geq 0.3 \times 10^9$ cells/L if rounded, and $\geq 0.45 \times 10^9$ cells/L or $\geq 0.5 \times 10^9$ cells/L if rounded) and
179 examining outcomes in ~~a~~ two subsets of patients: (1) after exclusion of those who initiated
180 inhaled corticosteroids (ICS) after their first asthma-related hospital admission and (2) after
181 exclusion of patients with a concomitant diagnosis of COPD.

182 Statistical analyses were conducted using IBM SPSS Statistics version 23 (IBM SPSS
183 Statistics, Feltham, Middlesex, UK) and R version 3.0.2 (The R Project for Statistical
184 Computing; <https://www.r-project.org/>). A statistically significant result was defined as $p \leq 0.05$.

185

186 **Results**

187 **Patients**

188 Of 146,485 patients in the CPRD with HES data linkage, 22,940 (16%) patients had at
189 least one hospital admission for asthma and ≥ 2 years of medical record data, and 3,611 patients
190 (16%) of those hospitalized had an eosinophil count recorded within 1 year before the

191 hospitalization (and no oral corticosteroid prescription within 2 weeks prior). Of these 3,611
192 patients, 2,613 patients (72%) were ≥ 5 years old, had active asthma, and were eligible for the
193 study (Fig 2).

194

195 **Fig 2. Flow Diagram Showing Selection of Eligible Patients from the Database.**

196 CPRD = Clinical Practice Research Database. HES = Hospital Episode Statistics. OCS = oral
197 corticosteroid. QOF = Quality Outcomes Framework.

198

199 In the study population, 482 of 2,613 patients (18%) were discharged from hospital on
200 the same day. Six patients died (one patient died 31 weeks after readmission for asthma and was
201 not censored; others were censored) during 1 year of follow up.

202 Characteristics of the total population with blood eosinophil count (n=2,613) and
203 ~~23,731~~13,016 patients with asthma who met all eligibility criteria except availability of blood
204 eosinophil count during baseline are presented in S2 Table. There were multiple statistically
205 significant differences between the two groups of patients. Eligible patients with recorded
206 eosinophil count were older than the ~~23,731~~13,016 patients without eosinophil count (median
207 age, ~~51~~50 vs. ~~31~~33 years), more commonly female (1,997/2,613, 76% vs.
208 ~~14,337~~23,731/~~7,542~~13,016, ~~60%~~58%), heavier (mean BMI ~~29.2~~29.1 vs. ~~26.5~~26.0 kg/m²), and
209 receiving a higher median ICS dose (~~262~~219 vs. ~~164~~132 μ g/day, fluticasone-propionate
210 equivalent) during the baseline year (S2 Table).

211 A high blood eosinophil count ($\geq 0.35 \times 10^9$ cells/L) was recorded during the year before
212 the hospital admission for 835 of 2,613 patients (32%). The high blood eosinophil cohort had a
213 median age of 45 (vs. 54 years in the cohort with eosinophil count of $< 0.35 \times 10^9$ cells/L) and
214 included proportionately fewer women and fewer overweight and obese patients (Table 1). In

215 addition, patients with eosinophil count $\geq 0.35 \times 10^9$ cells/L were more likely to be never-smokers
216 and to have a recorded diagnosis of rhinitis, atopic eczema, or nasal polyps.

217

218

219 **Table 1. Baseline Demographic and Clinical Characteristics.**

Variable	All patients (N = 2,613)	Blood eosinophil cohort		P value ^a
		<0.35x10 ⁹ cells/L (n = 1,778)	≥0.35x10 ⁹ cells/L (n = 835)	
Age				
Median (IQR)	51.0 (36.0-69.0)	54.0 (39.0-70.3)	45.0 (30.0-65.0)	<0.0001
5-12 years	56 (2.1)	17 (1.0)	39 (4.7)	<0.0001
13-17 years	77 (2.9)	31 (1.7)	46 (5.5)	
18-64 years	1,681 (64.3)	1,141 (64.2)	540 (64.7)	
≥65 years	799 (30.6)	589 (33.1)	210 (25.1)	
Female sex	1,997 (75.7)	1,392 (78.3)	585 (70.1)	<0.0001
Smoking status ^b				
Data available	2,597 (99.4)	1,771 (99.6)	826 (98.9)	
Current smoker	547 (21.1)	378 (21.3)	169 (20.5)	0.007
Ex-smoker	754 (29.0)	544 (30.7)	210 (25.4)	
Never smoker	1,296 (49.9)	849 (47.9)	447 (54.1)	
Body mass index ^b				
Data available	2,260 (86.5)	1,551 (87.2)	709 (84.9)	
Mean (SD)	29.2 (7.0)	29.6 (7.0)	28.4 (7.0)	<0.0001
<18.5 kg/m ²	78 (3.5)	38 (2.5)	40 (5.6)	<0.0001
≥18.5 kg/m ² to <25 kg/m ²	625 (27.7)	393 (25.3)	232 (32.7)	
≥25 kg/m ² to <30 kg/m ²	625 (27.7)	450 (29.0)	175 (24.7)	
≥30 kg/m ²	932 (41.2)	670 (43.2)	262 (37.0)	
Allergic/non-allergic rhinitis ^c	876 (33.5)	545 (30.7)	331 (39.6)	<0.0001
Atopic eczema ^c	927 (35.5)	595 (33.5)	332 (39.8)	<0.0001
Nasal polyps ^c	83 (3.2)	39 (2.2)	44 (5.3)	<0.0001
Chronic rhinosinusitis ^c	579 (22.2)	400 (22.5)	179 (21.4)	0.54
COPD ^c	284 (10.9)	192 (10.8)	92 (11.0)	0.87
GERD ^c	474 (18.1)	355 (20.0)	119 (14.3)	<0.001
Cardiovascular disease ^c	654 (25.0)	491 (27.6)	163 (19.5)	<0.0001
Charlson comorbidity index				
0	611 (23.4)	429 (24.1)	182 (21.8)	0.028
1-4	1,661 (63.6)	1,101 (61.9)	560 (67.1)	
≥5	341 (13.1)	248 (13.9)	93 (11.1)	
GINA step of asthma treatment ^b				
1	124 (4.7)	78 (4.4)	46 (5.5)	0.009
2	493 (18.9)	357 (20.1)	136 (16.3)	
3	468 (17.9)	298 (16.8)	170 (20.4)	
4	1,220 (46.7)	848 (47.7)	372 (44.6)	
5	308 (11.8)	197 (11.1)	111 (13.3)	
≥1 ICS inhaler prescribed	2,444 (93.5)	1,671 (94.0)	773 (92.6)	0.173

Daily dose of ICS ($\mu\text{g}/\text{day}$), median (IQR) ^d	262 (110-521)	263 (110-534)	247 (99-492)	0.041
≥ 1 SABA inhaler prescribed	2,432 (93.1)	1,646 (92.6)	786 (94.1)	0.144
Daily SABA dose, median (IQR) ^d	1.64 (0.82-3.55)	1.64 (0.66-3.29)	2.04 (0.82-4.11)	<0.0001
OCS daily dose (g), median (IQR)	0.55 (0-1.64)	0.55 (0-1.56)	0.55 (0-1.75)	0.139
No. severe asthma exacerbations				
0	747 (28.6)	516 (29.0)	231 (27.7)	0.25
1	848 (32.5)	589 (33.1)	259 (31.0)	
2	506 (19.4)	345 (19.4)	161 (19.3)	
3	266 (10.2)	174 (9.8)	92 (11.0)	
≥ 4	246 (9.4)	154 (8.7)	92 (11.0)	

220 Data expressed as No. (%) unless otherwise noted. COPD = chronic obstructive pulmonary disease. GERD =
 221 gastroesophageal reflux disease. GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; OCS = oral
 222 corticosteroid; SABA = short-acting β -agonist.

223 ^aP-value comparing blood eosinophil cohorts, computed from χ^2 test for categorical variables, or Mann-Whitney test,
 224 for continuous variables. Where variables are presented as both continuous and categorical, the p-value is from the
 225 Mann-Whitney test.

226 ^bThe closest BMI within 10 years of hospital discharge, and the smoking status closest to and within 5 years before
 227 hospital discharge, were included. The GINA [treatment](#) step was determined based on the last prescription before
 228 the hospitalization (S1 Table). The BMI categories applied to patients ≥ 18 years old; for children, BMI was not
 229 calculated because accurate information on age in months required to calculate BMI z-scores was not provided for
 230 privacy reasons.

231 ^cComorbidities were those with diagnostic Read code ever-recorded in the available data before hospital discharge.

232 ^dICS dose expressed as fluticasone propionate equivalent ($\mu\text{g}/\text{day}$), and one SABA dose defined as 200 μg in
 233 albuterol equivalents.

234

235

236 The likelihood of a blood eosinophil count being recorded was greater at dates closer to
 237 the hospital admission (S1 Fig). Patients with measurements within 4 weeks before the
 238 hospitalization were more likely to have a high blood eosinophil count (128/339, 38%) than
 239 those with measurement within a longer time period before the hospitalization (707/2274, 31%;
 240 $p=0.014$). [The length of time between recorded eosinophil count and admission with asthma as](#)
 241 [the primary diagnosis was greater in patients with high blood eosinophil counts than in patients](#)
 242 [without high counts, but the difference in distribution was not statistically significant \(144 days](#)
 243 [\[IQR, 56–250\] vs. 131 days \[58–229\], \$p=0.159\$ \).](#)

The median duration of hospitalization (2 nights) was the same in patients with and without a high blood eosinophil count; however, there were fewer patients with a high blood eosinophil count who had a long hospital stay (Table 2).

Table 2. Duration of Hospitalization.

Variable	All patients (N = 2,613)	Blood eosinophil cohort		P value ^a
		<0.35x10 ⁹ cells/L (n = 1,778)	≥0.35x10 ⁹ cells/L (n = 835)	
Nights in hospital, median (IQR)		2 (1–5)	2 (1–4)	
No. nights in hospital, n (%)				0.006
0	482 (18.4)	323 (18.2)	159 (19.0)	
1	529 (20.2)	349 (19.6)	180 (21.6)	
2	356 (13.6)	230 (12.9)	126 (15.1)	
3	281 (10.8)	182 (10.2)	99 (11.9)	
4	243 (9.3)	162 (9.1)	81 (9.7)	
5	149 (5.7)	99 (5.6)	50 (6.0)	
6	142 (5.4)	106 (6.0)	36 (4.3)	
≥7	431 (16.5)	327 (18.4)	104 (12.5)	

^aP-value comparing blood eosinophil cohorts computed from χ^2 test.

Readmissions by eosinophil cohort

Only 6 patients were readmitted to the hospital within 4 weeks of the first admission, with no significant difference between blood eosinophil cohorts (Table 23). At 1 year, 130 of 2,613 (5%) patients overall were readmitted for asthma, including a significantly greater percentage of patients with high vs. normal blood eosinophil count (Table 23; Fig 3). Patients with eosinophil count of $\geq 0.35 \times 10^9$ cells/L had a ~~45%~~49% higher adjusted risk of readmission to hospital for asthma in the first year of follow-up than patients without a high count (HR ~~1.45~~1.49; 95% CI ~~1.02~~1.04–2.13; ~~0.08~~0.029; p=0.04; Table 23).

260 **Table 23. Readmissions to Hospital within 4 Weeks and 1 Year and Hazard Ratios for**
 261 **Readmission in the High Eosinophil Count Cohort.**

Readmission	Eosinophil cohort		P value ^a	Adjusted HR (95% CI) for blood eosinophil count $\geq 0.35 \times 10^9/L^b$	P value
	<0.35x10 ⁹ cells/L (n = 1,778)	$\geq 0.35 \times 10^9$ cells/L (n = 835)			
With asthma as primary diagnosis (n = 2,613)					
Within 4 weeks	4 (0.2)	2 (0.2)	0.94	--	--
Within 1 year	75 (4.2)	55 (6.6)	0.009	1.49 (1.04-2.13) 1.45 (1.02-2.08)	0.029 0.040
By known smoking status (n = 2,597) ^c					
Never-smokers (n = 1,296)	29 (3.4)	30 (6.7)	0.007	2.16 (1.27-3.68) 1.95 (1.16-3.31)	0.005 0.013
Ex-smokers (n = 754)	19 (3.5)	13 (6.2)	0.010	1.49 (0.73-3.06) 1.52 (0.74-3.10)	0.27 0.25
Current smokers (n = 547)	27 (7.1)	12 (7.1)	0.99	1.00 (0.49-2.04) 0.97 (0.48-1.97)	0.99 0.94
Never/ex-smokers pooled (n = 2,050)	48 (3.4)	43 (6.5)	0.002	1.78 (1.17-2.73) 1.77 (1.16-2.70)	0.007 0.009
With respiratory condition other than asthma, and asthma as subsidiary diagnosis (n = 2,613)					
Within 4 weeks	22 (1.2)	8 (1.0)	0.53	--	--
Within 1 year	81 (4.6)	39 (4.7)	0.90	1.12 (0.76-1.65) 1.10 (0.75-1.63)	0.57 0.63

262 ^aP-value computed using χ^2 test.

263 ^bAdjusted for sex, age, smoking status, timing of blood eosinophil count measurement, duration of index
 264 hospitalization.

265 ^c16 patients with no recent record of smoking status were excluded from the analyses by smoking status.

266
267

268 **Fig 3. Kaplan-Meier Curves Describing the Cumulative “Survival” of a Readmission to**
 269 **Hospital for Asthma in the First Year After an Admission with Asthma as the Primary**
 270 **Diagnosis in Patients With and Without High Blood Eosinophil Count.**

271

272 Interaction with smoking status

273 ~~There was significant~~The effect ~~modification by of~~ current smoking was non-significant
274 (p=~~0.044~~0.073) when tested by including an interaction term for current smoking (yes/no) and
275 high blood eosinophil count (yes/no) into the model. The increased readmission rate with a high
276 blood eosinophil count was found only in non-smokers (HR 1.84; ~~1.21~~1.20–2.80; p=0.0054) and
277 not in current smokers (HR ~~0.81~~0.88; ~~0.41~~0.44–~~1.76~~1.61; p=~~0.55~~0.73). In this analysis of all
278 2,613 patients, 16 patients without recent, recorded smoking status were included as non-
279 smokers (never-smokers plus ex-smokers).

280 Results were similar for patients with known smoking status, with a significant
281 ~~95%~~216% higher adjusted risk of readmission for never-smokers with high blood eosinophil
282 count, and no additional risk for current smokers with high blood eosinophil count (Table 23).
283 Although the association was most pronounced in never-smokers, no significant difference in the
284 association was found between never-smokers and ex-smokers (p=~~0.80~~0.67) in the 2,050 patients
285 recorded as not currently smoking.

286

287 Sensitivity analyses

288 A high blood eosinophil count was recorded for 1,328 patients (51%) when defined as
289 $\geq 0.25 \times 10^9$ cells/L, and for 588 patients (23%) when defined as $\geq 0.45 \times 10^9$ cells/L. The
290 association between a high blood eosinophil count and readmission to hospital for asthma was
291 less pronounced and not significant for patients with blood eosinophil count of either $\geq 0.25 \times 10^9$
292 cells/L (HR=~~1.16~~1.17; 0.82–~~1.66~~1.65; p=~~0.39~~0.41) or $\geq 0.45 \times 10^9$ cells/L (HR=~~1.12~~1.15;
293 ~~0.75~~0.77–~~1.72~~1.69; p=~~0.50~~0.57; S3 Table). The association was also not significant in never-

294 smokers or in never/ex-smokers combined using either definition of high blood eosinophil count
295 (S3 Table).

296 A total of 169 of the 2,613 patients (6%) had no prescription for ICS in the baseline year
297 before being hospitalized for asthma; of the 169, 115 (68%) had ICS prescribed in the outcome
298 year. After exclusion of these 115 patients, HRs for the association with blood eosinophil count
299 of $\geq 0.35 \times 10^9$ cells/L slightly increased as compared with those for the full population (S3 Table).

300 The HR was 1.761.77 (95% CI, 1.141.15–2.722.70; $p=0.0090.010$) for never/ex-smokers
301 combined, which was very similar to the HR for never/ex-smokers combined of the full
302 population (1.771.78). However, effect modification by current smokers was not significant in
303 this subpopulation ($p=0.28102$).

304 Results of an additional subanalysis excluding patients with a concomitant diagnosis of
305 COPD showed no relevant difference in association for the remaining 2,329 patients (HR= 1.48;
306 95% CI 1.01–2.17, $p=0.045$; see S3 Table).

307

308 Discussion

309 In this large, historical cohort study, we found that patients who had a blood eosinophil
310 count of $\geq 0.35 \times 10^9$ cells/L recorded in the year preceding an asthma-related hospitalization had a
311 significantly greater risk of readmission for asthma during the year after they were discharged.
312 Few patients ($n=6$) were readmitted to hospital for asthma within 4 weeks after discharge, while
313 by 1 year after discharge, 5% (130 of 2,613) patients were readmitted for asthma. The greater
314 risk of readmission during 1 year follow-up was present only for patients with high blood
315 eosinophil count who were never- or ex-smokers (not for current smokers).

316 Our study is one of few studies examining hospital readmissions for asthma in a general
317 asthma population and in the real-life setting. Readmissions in the present study were
318 comparatively infrequent relative to results in other studies: for example, in one US study,
319 approximately 4% of patients were readmitted for an asthma exacerbation within 30 days [1921],
320 and in France from 2002–2005, 15% were readmitted for asthma within 1 year [2022]. The
321 overall rate of hospital admissions for asthma in England appears to be lower than for
322 Western Europe as a whole, the latter reported in 2004 to be 7% [1,23].

323 Other recent studies of hospital readmissions have been limited to patients on systemic
324 corticosteroids [89], have examined readmissions up to only 30 days [10,11,12,24,21], were
325 much smaller [2424], and/or were conducted at a single institution [22,23,25,26]. None of these
326 studies, nor others examining readmissions after 30 days [24-26,27-29], examined the association
327 of hospital readmissions with blood eosinophil count. While Gonzalez-Barcala et al. [13] in their
328 retrospective study at a single hospital in Spain found differently from the present study that
329 elevated eosinophil count was associated with a lower incidence of readmissions, it is difficult to
330 compare their study with ours because of differences in methods. For example, the reference
331 blood eosinophil count was that taken upon admission rather than before hospitalization during a
332 baseline year, and the length of the follow-up period for analyzing readmissions is unclear [13].

333 An interesting finding in the present study that requires further investigation is the effect
334 of smoking status on association of readmissions with eosinophil count. Cigarette smoking
335 increases levels of oxidative stress, alters airway immune responses, and increases risk of
336 hospitalization in patients with asthma [2730]. Westerhof et al. [2831] in their study of patients
337 with severe asthma found that frequent exacerbations were associated with blood eosinophil
338 count only in never smokers and not in ex-smokers, for whom blood neutrophil count was an

339 independent predictor of frequent exacerbations (smokers not studied). In our study, both never-
340 and ex-smokers (but not current smokers) who had a high eosinophil count were at greater risk of
341 asthma-related readmission, although for ex-smokers separately this association was not
342 statistically significant. Moreover, in our study the difference in association between non-
343 smokers (never-plus ex-smokers pooled) and smokers was large and statistically significant.
344 Clearly, additional work is needed to examine biomarker and peripheral blood cell profiles in
345 relation to smoking status and hospital readmissions and other asthma-related outcomes.

346 The median duration of hospitalization (2 nights) was the same in both normal and high
347 blood eosinophil cohorts; however, patients with a high blood eosinophil count were less likely
348 to have a hospital stay longer than 5 nights (17% vs. 24% of those without high eosinophil
349 count). This finding illustrates the conundrum of eosinophilic asthma: while it tends to be more
350 severe in terms of exacerbations and asthma control, eosinophilic asthma is also potentially more
351 responsive to therapies targeting type 2 inflammation, including ICS and biologics.

352 We speculated that the association between eosinophil count and readmission could be
353 diluted for patients with eosinophil count performed several months before the first admission;
354 therefore, we re-examined outcomes including only patients with eosinophil counts measured
355 close to the initial hospitalization to see if the association were stronger. However, when
356 selecting those with eosinophil count recorded within 4 months before hospitalization, the
357 numbers became small and associations non-significant, although the direction of the effect was
358 the same: for never- and ex-smokers pooled (n=915), the risk of readmission was 51% greater
359 but non-significant (adjusted HR 1.511.69; 0.540.60–4.764.25; p=0.3243).

360 A strength of this study is that we included a broad patient population with asthma, not
361 limited to those with severe asthma. We selected inclusion criteria to ensure that patients' asthma

362 was actively managed in advance of the hospital admission, thereby excluding patients
363 experiencing a first episode of asthma diagnosed at the time of admission. Moreover, we
364 required that patients had not received an oral corticosteroid prescription within 2 weeks before
365 the eosinophil count to obviate the eosinopenic effects of systemic corticosteroids [29,30,32,33].
366 The data sources we used are well-regarded and frequently employed for
367 pharmacoepidemiological studies [13-15,15-17,31,34]. The primary care data in the CPRD is
368 considered to be high-quality, with recording that has been standardized and improved since the
369 institution in 2004 of the UK Quality Outcomes Framework (QOF) [15,17], which provides
370 financial incentives for GPs to deliver quality care, including an annual asthma review covering
371 asthma control status, smoking, and inhaler technique. Detailed information about hospital
372 admissions was drawn from HES, a data warehouse linked to the CPRD [14,16].

373 Nevertheless, a limitation is that the study dataset comprised information collected for
374 clinical and routine use rather than specifically for research purposes. Moreover, prescriptions
375 for drugs prescribed by specialists are not reliably recorded in the CPRD. Therefore, we could
376 not evaluate treatment prescribed immediately after hospital discharge. However, the daily dose
377 of ICS prescribed by GPs in the year after admission was not significantly different between
378 patients with and without high eosinophil counts (median for both: 329 vs. 329 µg/day
379 fluticasone-equivalent, p=0.70, Mann-Whitney test). Finally, as for all observational studies,
380 there is the possibility of residual confounding from unrecognized and/or unmeasured factors.

381 A “count-response” association of blood eosinophil levels with risk of asthma
382 exacerbations has been reported in both an observational study [3] and for the placebo arm of
383 clinical trials [32,33,35,36]. Our study had insufficient patient numbers to assess the presence of a
384 count-response relationship with hospital readmissions using incremental categories to define

385 high eosinophil count. Our definition of $\geq 0.35 \times 10^9$ cells/L for high blood eosinophil count
386 captured a clear association of high blood eosinophil count with risk of readmission, while there
387 were fewer patients, hence limited statistical power, to evaluate the higher cut-point of $\geq 0.45 \times 10^9$
388 cells/L, although the direction of the effect was the same. Alternatively, new ICS use or better
389 ICS adherence after the index hospitalization might have reduced the effect of elevated
390 eosinophil count; however, it would not be easy to quantify this possibility in the framework of a
391 historical cohort study, and in spite of this possibility we found a strong association at the
392 $\geq 0.35 \times 10^9$ cells/L definition.

393 We did not exclude patients with a concomitant diagnosis of COPD; therefore,
394 approximately one-tenth of the study population appeared to have some form of physician-
395 diagnosed asthma-COPD overlap [3437], although these patients were too few to analyze
396 separately. However, the sensitivity analysis excluding these patients supported the findings for
397 the full population.

398 By necessity we were able to include only patients who had a recorded blood eosinophil
399 count, which is not routinely measured in clinical practice, a factor serving as a possible source
400 of selection bias and thereby limiting the generalizability of our findings. There were large
401 differences in baseline characteristics between the patients with available eosinophil count and
402 those without, who tended to be younger; more likely female, a current smoker, and of normal
403 weight; and less likely having comorbidities such as rhinitis, chronic sinusitis, gastroesophageal
404 reflux disease, and cardiovascular disease. The age differences were expected because older
405 people more frequently have full blood counts available. Further work is needed to examine the
406 use of blood eosinophil count in the clinical assessment of the full spectrum of patients with
407 asthma.

408 Tailoring asthma therapy using sputum eosinophil counts appears to be effective in
409 reducing exacerbations, particularly for adults with frequent exacerbations [3538]. Thus, blood
410 eosinophil count, more practical to measure than sputum eosinophil count, could play a role in
411 tailoring asthma therapy with the goal of reducing exacerbations, hence potentially hospital
412 readmissions. Moreover, further research is needed to identify the mechanism(s) behind the
413 increased risk of readmission associated with high blood eosinophil count, such as possible
414 undertreatment with ICS or insufficient effectiveness of ICS. In addition, more specifically, a re-
415 examination is needed of the absence of association with readmissions and high blood eosinophil
416 count in current smokers, as there was limited statistical power in this subgroup of patients,
417 reflected by the wide confidence interval.

418

419 **Conclusions**

420 A high blood eosinophil count in the year before an asthma-related hospitalization is
421 associated with increased risk of readmission within the following year. This risk was slightly
422 ~~increased-greater~~ in the subset of patients who were not new initiators of ICS treatment after their
423 index hospital admission, suggesting that this trait is only partially treatable with anti-
424 inflammatory therapy. This association was present only in non-smoking patients with high
425 blood eosinophil count. Our findings support the benefit of including a full blood count with
426 differential as a routine assessment in clinical practice for patients with not well-controlled
427 asthma. Moreover, our findings support the need for careful follow-up, with treatment
428 optimization, after hospital discharge for patients with asthma and preadmission high blood
429 eosinophil count.

430

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434

435

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555 **Supporting information**

556 **S1 Table. Definitions Applied for Global Initiative for Asthma (GINA) Treatment Step,**
557 **Determined Using Each Patient’s Last Prescription(s) Before the First Hospital Admission.**

558 **S2 Table. ~~Baseline~~ Demographic and Clinical Characteristics of All Eligible Patients with**
559 **Blood Eosinophil Count ~~During the Baseline Year~~ and of Patients Meeting All Eligibility**
560 **Criteria Except Availability of Eosinophil Count.^a**

561 **S1 Fig. Distribution of the Number of Days before Hospital Discharge on Which the Most**
562 **Recent Eosinophil Measurement Was Recorded.**

563 **S3 Table. Readmissions for Asthma within 1 Year and Hazard Ratios for Readmission in**
564 **the High Eosinophil Count Cohort: Sensitivity Analyses.**

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Review Comments to the Author

Please use the space provided to explain your answers to the questions above. You may also include additional comments for the author, including concerns about dual publication, research ethics, or publication ethics. (Please upload your review as an attachment if it exceeds 20,000 characters)

Reviewer #1: Thank you for conducting this retrospective review of admitted asthmatic patients. It was a pleasure to read.

Response to Reviewer #1, Comment 1: Thank you very much for your review and the positive feedback.

2. Could you please comment on the association between increased SABA use and decreased ICS dosages in the group with increased blood eosinophilia? What do you think this connection is? Your manuscript would be strengthened by exploring this in your Discussion.

Response to Reviewer #1, Comment 2: We have additionally analyzed the correlation between average ICS and SABA daily dose and found a weak positive correlation, similar in patients both with and without high blood eosinophil count (Spearman's rho, 0.31 and 0.37, respectively). Therefore, from Table 1, we cannot conclude that decreased ICS use results in increased SABA use at the patient level.

Although outside the scope of this manuscript, we can speculate about a reason for the slightly higher ICS doses in patients with low blood eosinophil count. Small effects of ICS on peripheral blood eosinophil counts may for example play a role. On the other hand, we know that high blood eosinophil counts are associated with more severe asthma, which could explain the greater use of SABA. This is the conundrum of eosinophilic asthma: it tends to be more severe in terms of exacerbations and asthma control but is also potentially more treatment responsive to T2 therapies including ICS and biologics.

Reviewer #2: REVIEW: 18-12337: Association between blood eosinophil count and risk of readmission for patients with asthma: historical cohort study

1. IMPORTANCE OF THE QUESTION OR SUBJECT STUDIED

An understanding of prognosis of asthma based on blood eosinophils count is very interesting topic for research, which has not been fully explained so far.

The objective is clearly stated.

Mention in the introduction section of some references with contradictory results in asthma patients according to blood eosinophils count could be useful to explain the rationale for carrying out this study. There are some studies where higher blood eosinophil count is related to more hospital admissions (Mäkelä MJ, Eur Clin Respir J. 2018 Apr 15;5(1):1458560.), however other authors show us the contrary (Gonzalez-Barcala FJ, Eur J Intern Med. 2018 Mar 4. pii: S0953-6205(18)30094-3.)

Response to Reviewer #2, Comment 1: Thank you for alerting us to these new publications. We have added them to the Introduction as suggested. The variable associations may relate to the conundrum mentioned in our response to the first reviewer's

second point, now included as an additional point in the Discussion (paragraph 5) with reference to the duration of hospitalization.

ADEQUACY OF APPROACH

In the methods section there are some weak points:

1. It is stated that “patients with asthma who had been admitted to hospital in England”. However, the meaning of hospital admission is not clear. What should be clarified is whether admission includes emergency room, hospital ward, intensive care unit or all of them

Response to Reviewer #2, Comment 1: We used the HES (Hospital Episode Statistics) Admitted Patient Care (APC) database, which contains records of patients who were admitted to a hospital ward, including patients who visited an emergency department before admission and patients who were admitted to an intensive care unit. We have now added this information to the Methods section.

2. Patients were included “if they had one or more valid blood eosinophil counts recorded during the year before the hospital admission”. However, if the patients have more than one valid blood eosinophil count which one was considered: the higher, the smaller, the mean value, the more recent..? It should be clarified.

Response to Reviewer #2, Comment 2: We used the most recent blood eosinophil count before the hospital admission, ie, closest to the admission, now clarified in the Methods section.

3. It is stated that the timing of blood eosinophil count was considered, but it is not explained how it was done?

Response to Reviewer #2, Comment 3: The likelihood of a blood eosinophil count being recorded was greater at dates closer to the hospital admission. We have now reported the median length of time between recorded eosinophil count and admission (with asthma as the primary diagnosis), which was greater in patients with high blood eosinophil counts than in patients without high counts, but the difference in distribution was not statistically significant (144 days [IQR, 56–250] vs. 131 [58–229], $p=0.159$). We included this variable as a confounder in the Cox regression model, as noted in the statistical analysis methods and in footnotes for Table 3 and S3 Table.

4. In page 8, line 155, it is stated “Global Initiative for Asthma [18] (GINA) step”. I think that the words “of treatment” are necessary after step.

Response to Reviewer #2, Comment 4: Thank you. We have now added “treatment” to GINA step wherever mentioned in the manuscript and supplemental information.

5. The statistical treatment seems adequate

6. Acceptable from an ethical point of view

Response to Reviewer #2, Comments 5 and 6: Thank you.

RESULTS

The results are well presented. However there some weak points too:

7. In table S2 there are data about the patients included and not included. Some statistical analysis to check the significance of the difference between these groups seems necessary

Response to Reviewer #2, Comment 7: We have reworked S2 table, as we discovered upon doing the statistical comparisons that some patients were represented more than once in the excluded column (ie, for additional hospitalization episodes at older ages). Moreover, for this new table we have included baseline characteristics for all patients *at the time of their first hospitalization*, in line with the study analyses, to obtain better insights regarding differences in patient characteristics between included vs. excluded patients (with vs. without eosinophil count). (As noted in the Methods section, we included the first hospitalization episode for patients meeting eligibility criteria.)

Therefore, we included the first hospital admission in the database for the 2,613 patients eligible for the study, regardless of availability of eosinophil counts in the prior year. For 2,076 of these 2,613 patients (79%) this admission was the same as the admission analyzed and reported in the main paper. Instead, for 537 patients (21%), the baseline characteristics refer to those at their first recorded hospitalization, while a later admission (when they had a blood eosinophil count recorded during the prior year) was used for the main analyses. Hence there are differences between baseline characteristics for eligible patients as reported in Table 1 versus S2 Table.

We have now added p-values to S2 Table and have noted that there were multiple statistically significant differences, summarized in the Results section, between included and excluded patients. The age differences were expected because older people more frequently have full blood counts available.

8. There are some important data lacking: the duration of hospital stay is important for readmissions

Response to Reviewer #2, Comment 8: Thank you for this important observation. Please see the hospitalization durations now added as a new Table 2. Although the median admission duration (2 nights) was the same in patients with and without a high eosinophil count, there were fewer patients with a long stay in hospital among those with a high blood eosinophil count. Adjustment for this variable in the analyses resulted in a slightly stronger association with risk of readmission (HR=1.49; 95% CI 1.04-2.13; p=0.029).

We have revised Table 3 (formerly Table 2) and S3 Table, showing results adjusted for duration of the first hospitalization.

9. ... and treatment after hospital discharge is very important too

Response to Reviewer #2, Comment 9: Prescriptions for drugs prescribed by specialists are not reliably recorded in the CPRD. Therefore, we cannot provide accurate information on treatment immediately after hospital discharge. However, the average daily dose of ICS prescribed by GPs in the year after admission was not significantly different between patients with and without high eosinophil counts (median for both: 329 vs 329 µg/day fluticasone-equivalent, p=0.70, Mann-Whitney test).

In our sensitivity analysis excluding patients who initiated ICS after hospital admission in the first year of follow-up, we found a slightly increased association of high blood eosinophils with readmissions.

We have included these points and the year-2 ICS doses in the Discussion section.

10. In table 2 the analysis of readmissions is not adjusted by obesity. It could be relevant because the impact of obesity could be different in eosinophilic and non-eosinophilic asthma (Mukadam S1, , J Asthma. 2017 Aug 28:1-6)

Response to Reviewer #2, Comment 10: We have evaluated confounding by BMI by including a variable with categories underweight, normal weight, overweight, or obesity into the Cox regression model and found no relevant (<2%) change in the coefficient for the association between a high eosinophil count and time to the first hospital admission. When including a dichotomous variable obesity (yes vs. no) there was only an 0.07% change in coefficient. The main analyses were therefore not adjusted by obesity or BMI. However, there was relevant confounding in the sensitivity analysis using a higher cut-point. These analyses were therefore adjusted for BMI, as noted in the footnote to S3 Table.

DISCUSSION

10. Considering that smokers are included and 31% are 65 years old or more, some doubts emerge about the possibility of inclusion of COPD patients. The accuracy of the diagnosis from primary care should be discussed.

Response to Reviewer #2, Comment 10: We have now performed and added the results and discussion of an additional sensitivity analysis excluding patients with a concomitant COPD diagnosis. We found no relevant difference in association for the remaining 2,329 patients: HR= 1.48; 95% CI 1.01–2.17, $P=0.045$, S3 Table).

11. The significant differences between patients included and not included should be cited as a limitation, and as a possible source of inclusion bias.

Response to Reviewer #2, Comment 11: This fact was indeed included in the Discussion as a factor limiting generalizability of study results, and we have now added the reviewer's point that it could serve as a possible source of selection bias.

12. The readmission rate is quite low. Could the authors explain, at least hypothetically the reason for this result?. Could it be due to some selection bias based on lack of accuracy of diagnosis?. Or could it be due to the inclusion of mild exacerbations treated in the emergency room which didn't need hospital ward admission?

Response to Reviewer #2, Comment 12: Our understanding is that hospitalization rates for asthma are generally lower in the UK than in other countries. We do not believe that readmission rates were low because of selection bias or other factors, because the HES data are considered to be reliable.

By our calculations, the crude annual admission rate in England is approximately 2.5%, including day cases. (This is calculated from the data presented in the first paragraph of the Introduction: “Approximately 83,000 hospital episodes (including inpatient, day-case, and intensive care episodes) were recorded as related to asthma in England in 2011-2012, representing approximately 3.3 million patients with clinician-reported, diagnosed-and-treated asthma in England during that time.”) Instead, according to the earlier global Asthma Insights and Reality surveys (Rabe et al. JACI 2004; 114:40-47), the hospitalization rate in western Europe is 7% and that in the US is 9%.

We have expanded the section on rates of readmissions in the second paragraph of the Discussion accordingly.

13. The conclusions are clear and supported by the data presented.

Response to Reviewer #2, Comment 13: Thank you.

REFERENCES

14. The references are relevant and updated. I think there are a few references lacking

Response to Reviewer #2, Comment 14: We have added the references suggested by the reviewer (new references 6 and 13) in addition to another reference (23) supporting the rates of hospitalization in Western Europe.

GRAMMAR AND STYLE

Writing clear and easy to follow

English language satisfactory

ABSTRACT

Adequate and well structured