Asthma Phenotypes and COVID-19 Risk: A Population-based Observational Study

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Short running title

Asthma phenotypes and COVID-19 risk

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Authors’ contributions

CIB conceived the study and analysed the data. CIB, PC and JAW contributed substantially to study design, data interpretation and writing.

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Data sharing

Data are available on request from the Clinical Practice Research Datalink (CPRD). Their provision requires the purchase of a license, and our license does not permit us to make them publicly available to all. We used data from the version collected in July 2020 and have clearly specified the data selected in our Methods section. To allow identical data to be obtained by others, via the purchase of a license, we have provided the code lists. Licences are available from the CPRD (http://www.cprd.com): The Clinical Practice Research Datalink Group, The Medicines and Healthcare products Regulatory Agency, 10 South Colonnade, Canary Wharf, London E14 4PU.

At A Glance

What is the current scientific knowledge on this subject?

Some COVID-19 studies have suggested patients with more severe asthma are at higher risk of adverse outcomes but whether this is specific to COVID-19 has not been addressed and the ability to phenotype asthma patients has been limited due to lack of data. Furthermore, there have been conflicting findings regarding the role of type-2 inflammation.

What does this study add to the field?

This large longitudinal study, using individually linked community, hospital and SARS-CoV2 test data, has found asthma patients with higher use of asthma maintenance medication and more frequent exacerbations were significantly associated with severe COVID-19 outcomes, including hospital admission, ICU admission and death; the same patients were also associated with a higher risk of
hospitalisation with influenza and pneumonia. Patients with markers suggestive of having type-2 inflammation were not found to be associated with more severe COVID-19 outcomes.
Abstract

**Rationale:** Studies have suggested some asthma patients are at risk of severe COVID-19, but they have had limited data on asthma phenotype and have not considered if risks are specific to COVID-19.

**Objectives:** Determine the effect of asthma phenotype on three levels of COVID-19 outcomes. Compare hospitalisation rates to influenza and pneumonia.

**Methods:** Electronic medical records were used to identify asthma patients and match them to the general population. Patient-level data were linked to Public Health England SARS-CoV-2 test data, hospital, and mortality data. Asthma was phenotyped by medication, exacerbation history, and type-2 inflammation. The risk of each outcome, adjusted for major risk factors, was measured using Cox regression.

**Measurements and Main Results:** 434,348 asthma and 748,327 matched patients were included. All asthma patients had a significantly increased risk of a GP-diagnosis of COVID-19. Asthma with regular inhaled corticosteroid (ICS) use (HR=1.27, 95%CI=1.01-1.61), intermittent ICS + add-on asthma medication use (HR=2.00, 95%CI=1.43-2.79), regular ICS + add-on use (HR=1.63, 95 CI=1.37-1.94), or with frequent exacerbations (HR=1.82, 95% CI=1.34-2.47) was significantly associated with hospitalisation. These phenotypes were significantly associated with influenza and pneumonia hospitalisations. Only patients with regular ICS + add-on asthma therapy (HR=1.70, 95%CI=1.27-2.26) or frequent exacerbations (HR=1.66, 95%CI=1.03-2.68) had a significantly higher risk of ICU admission or death. Atopy and blood eosinophil count were not associated with severe COVID-19 outcomes.

**Conclusions:** More severe asthma was associated with more severe COVID-19 outcomes, but type-2 inflammation was not. The risk of COVID-19 hospitalisation appeared to be similar to the risk with influenza or pneumonia.

**Word count = 250 (maximum allowed=250)**
Keywords: asthma, SARS-CoV-2, COVID-19, disease severity, mortality, allergic rhinitis, influenza, pneumonia
Introduction

The effect of SARS-CoV2 in asthma continues to be unclear, one and half years after the start of the COVID-19 pandemic. Health organisations initially declared asthma patients to be highly vulnerable but epidemiological studies from the earliest outbreak centres indicated they had reduced susceptibility\textsuperscript{1-3}. Subsequently, several pre-clinical studies provided some biological plausibility to a protective effect, indicating type-2 inflammation and corticosteroid use could downregulate key SARS-CoV2 entry genes\textsuperscript{4-7}.

Two large U.K. consortia were established to determine risk factors for COVID-19 related death. Using primary care electronic medical records, OpenSAFELY reported no associated risk or protective effect with asthma, except for a slight increase in risk for patients with more severe asthma, defined by a prescription for a short course of oral corticosteroids in the year before study entry\textsuperscript{8}. ISARIC (International Severe Acute Respiratory and emerging Infection Consortium), addressed the risk of in-hospital death from COVID-19; only asthma patients using three maintenance asthma medications were at significant risk\textsuperscript{9,10}.

The OpenSAFELY and ISARIC cohorts were also used to investigate the relationship between mortality and inhaled corticosteroid (ICS) use. While ISARIC found a reduced risk of in-hospital death associated with recent ICS use, OpenSAFELY found an increased mortality with regular high dose ICS as compared to short-acting beta-agonist (SABA) use alone\textsuperscript{10,11}. To examine the influence of allergic asthma, two other large cohorts have been used; the population-based U.K. Biobank database and the South Korean national health insurance claims-based database. Both studies found that non-allergic asthma was significantly associated with severe outcomes but differed on their findings for allergic asthma\textsuperscript{12,13}.

These studies have been limited by access to either only primary care or secondary care patient information. Here, we build on and improve our current knowledge through individual-level linkage of primary care data to data on SARS-CoV2 test results, hospital and intensive care admissions and mortality across a longer period than previous studies. This has allowed more in-depth asthma
phenotyping and measurement of outcomes. We have also more comprehensively addressed the
effect of type-2 inflammation, assessing the effect of atopy and blood eosinophil count in asthma, and
patients with another type-2 inflammatory condition, allergic rhinitis. Lastly, we have compared the
effect of SARS-CoV2 infection to that of two other respiratory infections, pneumonia, and influenza.

Methods

Data sources

We used the Clinical Practice Research Datalink (CPRD) Aurum, a database of de-identified U.K.
primary care electronic medical records. CPRD covers approximately 19% of the population, is one of
the largest longitudinal healthcare databases worldwide and has been validated extensively14. CPRD
data were individually linked to Hospital Episode Statistics data (hospital admissions for England, HES),
socioeconomic data (Index of Multiple Deprivation, IMD), mortality data (Office of National Statistics,
ONS) and two Public Health England (PHE) databases: the Second Generation Surveillance System data
(laboratory test results for SARS-CoV2 in hospital patients and NHS key workers, SGSS) and the COVID-
19 Hospitalisations in England Surveillance System data (outcome information including intensive care
admission, discharge or death, for patients admitted to hospital with confirmed COVID-19, CHESS)15.

Study population and design

Adults (≥18 years) contributing to CPRD Aurum from 1st February 2020, with linked HES-ONS-PHE data,
and at least 12 months of data before study entry, were eligible for inclusion. Follow-up ended at the
earliest of the following: study end date (26th June 2020), transfer out of practice, last GP practice data
collection date, or death. The first wave of the pandemic in the U.K. occurred between March 2020
and May 2020 inclusive16; the study follow-up period is inclusive of these dates.

Two different matched cohorts were derived, one each for asthma and allergic rhinitis. Each exposed
patient was matched to at least one (maximum three) unexposed patient(s) drawn from the rest of
the CPRD population with the same year of birth, sex, and GP practice. These unexposed patients are
termed ‘general population’. Asthma patients were identified using a validated algorithm that identified patients using specific asthma codes, the three most commonly used codes were ‘asthma’, ‘asthma annual review’ and ‘asthma monitoring’, while those with allergic rhinitis were identified using specific Read codes (see below), recorded within 3 years of 1st February 2020. Asthma patients had to have at least one prescription for a relevant medication (inhaler or oral asthma medication) in the year before study start (baseline year). Allergic rhinitis patients had to have been prescribed an antihistamine and a nasal corticosteroid in the baseline year. In the asthma matched cohort, patients from both populations were excluded if they had a COPD co-diagnosis. In the allergic rhinitis matched cohort, patients were excluded if they had a COPD or asthma co-diagnosis.

Outcomes

Three main COVID-19 outcomes were assessed: (i) GP diagnosis (suspected or confirmed COVID-19; CPRD and SGSS), (ii) hospital admission for COVID-19 (ICD-10 codes U07.1 or U07.2, HES and CHESS) and (iii) intensive care admission or death (HES, CHESS and ONS).

Two additional outcomes were assessed in the asthma cohort in order to better understand the association with a GP diagnosis: (a) GP consultation for covid advice or being a COVID-19 contact and (b) receiving a confirmed COVID-19 diagnosis in those that initially received a suspected COVID-19 diagnosis.

To compare the magnitude of association between asthma phenotype and COVID-19 to other respiratory infections, we measured hospitalisation for pneumonia (J18.9) and influenza (J09-J11).

We also undertook three negative control analyses, using the same model in the same cohort but measuring the effect estimates for negative control outcomes, type 2 diabetes (E11-E14), myocardial infarction (I21-I23) and fracture of the forearm (S52). These outcomes are common in adults of all ages and not thought to be associated with asthma phenotype; if a similar association with asthma phenotype was found this would suggest residual confounding. The control outcomes were measured
between 1st February 2019 and 26th June 2019. As a sensitivity analysis, influenza was also measured during the seasonal influenza season, 1st December 2018 to 26th April 2019.

**Exposures**

Asthma was phenotyped by medication use (type and frequency), exacerbation history and type-2 inflammation (atopy history and blood eosinophil count). For medication use, asthma was categorized by prescriptions in the baseline year: SABA only, ICS +/- SABA, ICS + an additional (‘add-on’) asthma maintenance medication (inhaled long-acting beta-agonist, oral leukotriene receptor antagonist, or oral theophylline). ICS users were further categorised by the number of prescriptions in the baseline year, using an arbitrary cut-off based on clinical experience of 1-3 prescriptions (‘intermittent’ ICS users) or ≥4 prescriptions (‘regular’ ICS users). This dichotomization was intended as a further proxy for asthma severity, alongside the type of medication used. Asthma patients were additionally categorised according to exacerbations in the baseline year: (i) 1 GP-managed, or (ii) >1 GP-managed or ≥1 hospital admission for asthma in the past 5-years; the latter stratum was labelled as ‘frequent exacerbations’. Our previous work found hospital admissions up to 5 years prior were associated with a significant risk of a future exacerbation. GP-managed exacerbations were defined as a prescription of a short course of oral corticosteroids (OCS). Lastly, asthma was categorised as atopic or not; atopy included a diagnosis of allergic rhinitis, allergic dermatitis, eczema, house dust mite allergy, animal allergy or food allergy. Blood eosinophil counts were taken as the maximum absolute value from all values within 24 months before the study start date.

**Covariates**

Confounders were considered based on previous studies and included as covariates in all models. Code lists were used to identify covariates, ethnicity was obtained from HES data variable. Obesity was defined as a body mass index ≥30 kg/m².

**Statistical analysis**
Patients’ characteristics were reported using descriptive statistics and Kaplan-Meier plots were used to show time to outcome. We used a cause-specific competing risk analysis, with patients dying from non-COVID-19 causes censored on their date of death. We used multivariable Cox’s proportional hazard models, stratified by matched set (matched on age, sex, and GP practice), with time in study as the time scale, to estimate hazard ratios (HRs) for the association between each respiratory condition and time to first event for each outcome. The models were adjusted for ethnicity, socioeconomic status, obesity, cardiac disease, diabetes, cerebrovascular accident (CVA), dementia, cancer, and chronic renal failure (CRF). Asthma models were additionally adjusted for atopy, respiratory disease severity and exacerbation history. We also undertook an interaction analysis between atopy and each outcome.

Four sensitivity analyses were conducted; (i) to circumvent the issue of misclassification of asthma, the asthma cohort was stratified by age, using a cut-off of 55 years; (ii) only confirmed GP codes were included as a GP diagnosis of COVID-19 (iii) only deaths were included in the last COVID-19 outcome, i.e., ICU admissions were removed; (iv) for the influenza model, instead of applying the equivalent dates of the COVID-19 model to the year 2019, the same length of time was used but during the peak influenza season (1st December – 26th April). In all models, patients with missing ethnicity data were included and recorded as ‘unknown’, patients with missing BMI were presumed non-obese, (missing BMI data in primary care is expected to be missing not at random\(^2\)), and patients with missing IMD data (0.1%) were excluded. We assessed the proportional hazards assumption for all models by testing that the Schöenfeld residuals were independent of time, through inspecting plots against time and statistical tests.

A mixed-effects logistic regression model (GP practice as a random effect) was used to measure the association with receiving a confirmed COVID-19 diagnosis in the subgroup of the asthma cohort that received a suspected COVID-19 GP diagnosis; the sample size was insufficient for a matched Cox model. The model was adjusted for sex, age (as a transformed continuous variable), ethnicity,
socioeconomic deprivation, obesity, atopy, cardiac disease, diabetes, CVA, CRF, dementia and cancer. We used a restricted cubic spline with three knots (0.10, 0.29, 0.60 x10^9/L) to evaluate the non-linear association between blood eosinophil count and risk of ICU or death in asthma patients only, using complete case analysis; the model was adjusted for sex, age, ethnicity, socioeconomic deprivation, obesity, cardiac disease, diabetes, CVA, CRF, dementia and cancer. All statistical analyses were performed using STATA 16 (StataCorp, College Station, Tex).

**Ethical approval**

A protocol for this research was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA Database Research (protocol number 20_096). Generic ethical approval for observational research using the CPRD with approval from ISAC has been granted by a Health Research Authority (HRA) Research Ethics Committee (East Midlands – Derby, REC reference number 05/MRE04/87).

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**Results**

**Patient characteristics**

There were 1,182,675 patients in the asthma cohort (434,348 asthma and 748,327 matched general population) and 157,247 patients in the allergic rhinitis cohort (41,890 allergic rhinitis and 115,357 matched general population) (Figure 1). Demographic and clinical characteristics of each cohort are shown in Table 1 and S1. The median age of the asthma cohort was 48.5 years and 42.5% were male, 59.2% of the asthma patients were using ICS and 19.2% had an exacerbation in the year prior.

**Temporal distribution and frequency of COVID-19 outcomes**
The distribution of all three outcomes followed a similar pattern, although deaths lagged hospital admissions; peaks occurred in April and March 2020 (Supplemental Figures S1-3). There were more COVID-19 GP-diagnoses (1.85% of asthma patients, 1.94% of allergic rhinitis patients) than hospital admissions (0.23% of asthma patients, 0.15% of allergic rhinitis patients) or ICU admission/death (0.08% of asthma patients, 0.03% of allergic rhinitis patients) (Tables 1 and S1). Time to each of the COVID-19 outcomes for the asthma cohort is shown in Supplemental Figure S4. Compared to patients who died during or after a hospital admission, those who died without a prior hospital admission were older with a higher proportion with dementia and CVA (Table S2).

Association between asthma and GP COVID-19 diagnosis

All types of asthma, regardless of medication phenotype, were significantly associated with receiving a GP diagnosis of COVID-19 (adjusted HR, 95% CI: SABA only = 1.63, 1.53-1.74; intermittent ICS = 1.42, 1.29-1.56; regular ICS = 1.41, 1.28-1.55; intermittent ICS + add-on = 1.79, 1.61-1.99; regular ICS + add-on = 1.73, 1.62-1.85; 1 exacerbation = 1.42, 1.29-1.58; more frequent exacerbations = 1.76, 1.57-1.97; Figures 2, Supplemental Figure S5 and Table S3) and with consulting their GP for COVID-19 advice or contact (Supplemental Figure S6). All asthma patients diagnosed with suspected COVID-19, regardless of medication phenotype, had a significantly lower odds of receiving a confirmed COVID-19 diagnosis (Supplemental Figure S7). Due to the low availability of testing within the community during the first wave of the pandemic in the U.K., only 9.4% of GP codes were confirmed COVID-19. A sensitivity analysis only including confirmed codes as a GP diagnosis had little impact on the effect estimates (Supplemental Figure S8).

Association between asthma and hospital admission, ICU admission or death

Asthma patients in whom there were significant associations with COVID-19 hospital admission were regular users of ICS (adjusted HR=1.27, 95% CI=1.01-1.61), intermittent users of ICS + an add-on therapy (adjusted HR=2.00, 95% CI=1.43-2.79), regular uses of ICS + add-on therapy (adjusted HR=1.63, 95% CI=1.37-1.94) or those with more frequent exacerbations (adjusted HR=1.82, 95%
Asthma patients in whom there were significant associations with COVID-19 ICU admission or death were regular users of ICS + an add-on therapy (adjusted HR=1.70, 95% CI=1.27-2.26) or those with more frequent exacerbations (adjusted HR=1.66, 95% CI=1.03-2.68) (Figures 2, Supplemental Figure S5 and Table S5).

Sensitivity analyses, only including death (excluding ICU admissions Supplemental Figure S9) and stratifying the asthma cohort by age (Supplemental Figure S10 and S11), found that associations with the same asthma phenotypes persisted, although, the cumulative proportion of ICU admissions/death during the study period was considerably higher in patients aged 55 years or more (under 55 years = 63 (0.06%) ICU admissions/deaths, 55 years or more = 683 (0.15%) ICU admissions/deaths).

Association between asthma and non-COVID-19 hospital admissions

The asthma patients with a significantly increased risk of COVID-19 hospital admission had a significantly higher risk of pneumonia and influenza admissions, with similar levels of relative risk, but lower rates of events (adjusted HR, 95% CI: (i) Influenza, SABA only = 1.02, 0.45-2.29; intermittent ICS = 0.96, 0.26-3.48; regular ICS = 1.17, 0.34-3.96; intermittent ICS + add-on = 2.72, 0.51-14.4; regular ICS + add-on = 3.82, 1.76-8.26; 1 exacerbation = 5.18, 0.96-28.1; more frequent exacerbations = 4.20, 1.16-15.22; (ii) Pneumonia, SABA only = 1.34, 0.61-2.98; intermittent ICS = 1.39, 0.40-4.82; regular ICS = 4.10, 1.04-15.79; intermittent ICS + add-on = 8.43, 1.50-47.33; regular ICS + add-on = 7.53, 3.07-18.46; 1 exacerbation = 2.80, 0.84-9.29; more frequent exacerbations = 2.53, 0.61-10.38; Figure 3 and Table 2). As sensitivity analyses, using age cut-off of 55 years (Supplemental Figure S12) or using peak seasonal influenza months (data not shown), there was little change to the effect estimates but a small increase in the rates of influenza cases during peak seasonal influenza months (Table 2).

No asthma patient groups had a significantly greater risk of the negative control outcomes of hospital admission for diabetes, myocardial infarction, or right arm fracture (Supplemental Figure S13).

Association between atopy and COVID-19 outcomes
In the asthma cohort, atopy was significantly associated with a GP-diagnosis but not with hospitalisation or ICU admission or death (Figures 2, Supplemental Figure S5 and Table S6). Atopy did not modify the association between asthma severity and outcomes (p<0.05). There were 290,639 (66.9% of total asthma study population) patients included in the analysis of blood eosinophil count. Patients with an eosinophil count were broadly similar in characteristics to the total asthma study population but were slightly older, more often female, more of white ethnicity, had more severe asthma, less obesity, less cardiac disease, and less diabetes (Table S6) Eosinophil count was not significantly associated with a COVID-19 hospital admission, ICU admission or death (Figure 4).

Allergic rhinitis was significantly associated with receiving a GP diagnosis, but not with hospital admission, ICU admission or death (GP diagnosis, adjusted HR = 2.17, 95% CI 1.92-2.43; hospital admission, adjusted HR = 1.37, 95% CI 0.91-2.06; ICU admission or death = 0.93, 95% CI 0.34-2.56; Supplemental Figure S14).

Discussion

In our asthma cohort, comprised of over 1 million asthma and matched general population patients, there was an increased risk of GP-diagnosed COVID-19 for all asthma phenotypes, including those prescribed SABA alone and those with atopy. This could represent a greater risk of infection with SARS-CoV2 for asthma, but there was also a significant association with GP consultation for advice on COVID-19 and reporting exposure to COVID-19. In addition, asthma patients were significantly less likely to have their suspected COVID-19 diagnosis confirmed, indicating a higher risk of false positive labelling of COVID-19 in asthma than the general population. Put together, these findings suggest asthma patients had increased healthcare seeking behaviour and GPs a lower threshold to diagnose COVID-19 in them. These healthcare behaviours are likely to reflect the initial global concern that asthma would be associated with severe COVID-19 outcomes.

Next, we examined whether asthma patients were more likely to be admitted to hospital with COVID-19, after accounting for all other major risk factors. We found those patients with regular ICS use,
intermittent or regular use of ICS + an add-on therapy, or those with frequent exacerbations, were at a significantly higher risk of hospitalisation. Lastly, we assessed the risk of ICU admission or death. Patients with regular use of ICS + add-on therapy had a 70% increased risk and those with frequent exacerbations had a 66% increased risk, although the absolute risk was low. It is worth noting that asthma patients did not change their pattern of inhaler prescriptions during this time period, except for a brief increase in inhaler prescriptions at the beginning of the first wave in those with mild asthma\textsuperscript{21}.

Our findings suggest that COVID-19 outcomes are related to asthma severity, as defined by use of maintenance inhaler medication and exacerbation history. While a large systematic review did not find an association with asthma and COVID-19, this may have been because asthma was considered as a homogenous condition without phenotyping\textsuperscript{22}. Analysis of the large OpenSAFELY and ISARIC datasets did apply phenotyping, and although limited by the data available on the patients’ asthma they found more severe asthma was linked to COVID-19 related mortality. The OpenSAFELY study, including community patients, only dichotomized asthma severity by prior prescriptions of oral corticosteroids from their GP\textsuperscript{11}. The ISARIC study, of a hospitalised cohort, was only able to stratify asthma patients by their recent medication use\textsuperscript{10}. Importantly, both studies considered patients with asthma separately from patients with both asthma and COPD, as we have done here. But these earlier studies were not able to address the risk of hospitalisation or diagnoses in primary care. To phenotype asthma patients in the present study, we had access to all medications, frequency of prescriptions and treatment of exacerbations within both primary and secondary care. This more granular phenotyping has further added to the evidence that milder asthma is neither protective, nor associated with severe COVID-19 outcomes. Interestingly, age did not modify the relative risk between asthma phenotypes and ICU admission or death, but there were considerably more deaths in the older age group.

The pattern of hospitalisation risk for the different asthma phenotypes was also apparent when examining the risk for pneumonia and influenza, but not for diabetes, myocardial infarction or
fractures. This finding parallels and builds upon the results from another study from the OpenSAFELY consortium\textsuperscript{23}, where the authors demonstrate that for many recognised COVID-19 risk factors (including age, male sex and obesity), the risk of death is a magnification of the risk that would be expected from non-COVID-19 death. In contrast, although asthma patients with recent oral-steroid use had a significantly raised risk of COVID-19 death, they had a much lower risk of non-COVID-19 death, suggesting the mortality risk was particular to COVID-19\textsuperscript{23}.

While the incident rate of hospitalisation was considerably higher for COVID-19 than either pneumonia or influenza in the overall population, the elevated adjusted association between asthma and risk of hospitalisation was similar between the three respiratory infections. This finding even held true for those younger patients, aged under 55 years.

We found no association between severe COVID-19 outcomes and variables representing probable type 2-inflammation. There was no association in asthma patients with atopy or a raised blood eosinophil count, or in patients with allergic rhinitis. This is consistent with a large study using the UK Biobank dataset which assessed the risk of allergic asthma\textsuperscript{12}. However, two studies published using the SARS-CoV-2 positive patients from the South Korean Health Insurance Review & Assessment Service, found an elevated risk of severe COVID-19 outcomes with allergic asthma and chronic rhinosinusitis\textsuperscript{13,24}. Neither study accounted for asthma severity which may have confounded associations.

**Limitations**

The data in this study are only from the first wave of COVID-19 in the U.K., before the availability of COVID-19 vaccination and before the routine use of corticosteroids and other treatments in hospitalised patients; associations with outcomes may have changed subsequently. This study may share the limitations of all observational research, including residual confounding and bias, and observational studies, such as this one, cannot be used to demonstrate causality. Patients may have inaccurate diagnoses of respiratory conditions or may not be using the medications prescribed by their
GP. We have attempted to reduce misclassification in asthma by excluding patients with a co-diagnosis of COPD and carrying out a sensitivity analysis using an age cut-off of 55 years (below this age, misclassification with COPD is rare. We did not have information on adherence to medication or subjective level of disease control. We did not include smoking as a variable due to the large amount of missing data on current smoking history, particularly in the general population. Another limitation is misclassification of outcomes; mortality data were obtained from death certificates written by physicians, at a time when there was a shortage of PCR tests in the U.K.

Conclusion

All asthma phenotypes were associated with an increased risk of receiving a GP-diagnosis of COVID-19 during the first wave of the pandemic in the U.K., this may have been related to behavioural factors. Higher use of asthma maintenance medication and a history of frequent exacerbations were significantly associated with severe COVID-19 outcomes including hospital admission, ICU admission and death. Measurements of type 2 inflammation were not significantly associated with severe COVID-19 outcomes. Those with higher medication use, or frequent exacerbations, were associated with a similar increased risk of hospitalisation for influenza, pneumonia, and COVID-19, although the incidence was much higher for COVID-19. Asthma patients who regularly use ICS and an add-on therapy or have frequent exacerbations, are at higher risk of developing adverse consequences from COVID-19 and influenza than the general population, after accounting for other recognised risk factors; such patients should consider vaccination against both diseases.
References

1. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA.* 2020;323(16):1574-1581.

2. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA.* 2020;323(20):2052-2059.

3. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *The Journal of allergy and clinical immunology.* 2020;146(1):110-118.

4. Finney LJ, Glanville N, Farne H, et al. Inhaled corticosteroids downregulate the SARS-CoV-2 receptor ACE2 in COPD through suppression of type I interferon. *bioRxiv.* 2020:2020.2006.2013.149039-142020.149006.149013.149039.

5. Peters MC, Sajuthi S, Deford P, et al. COVID-19-related genes in sputum cells in asthma: Relationship to demographic features and corticosteroids. *American Journal of Respiratory and Critical Care Medicine.* 2020;202(1):83-90.

6. Jackson DJ, Busse WW, Bacharier LB, et al. Association of Respiratory Allergy, Asthma and Expression of the SARS-CoV-2 Receptor, ACE2. *Journal of Allergy and Clinical Immunology.* 2020;146(1):203-206.e3.

7. Kimura H, Francisco D, Conway M, et al. Type 2 inflammation modulates ACE2 and TMPRSS2 in airway epithelial cells. *J Allergy Clin Immunol.* 2020;146(1):80-88.e88.

8. Williamson EJ, Walker AJ, Bhaskaran K, et al. OpenSAFELY: factors associated with COVID-19 death in 17 million patients. *Nature.* 2020;584(7821).
9. Docherty AB, Harrison EM, Green CA, et al. Features of 20133 UK patients in hospital with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol: Prospective observational cohort study. The BMJ. 2020;369.

10. Bloom CI, Drake TM, Docherty AB, et al. Risk of adverse outcomes in patients with underlying respiratory conditions admitted to hospital with COVID-19: a national, multicentre prospective cohort study using the ISARIC WHO Clinical Characterisation Protocol UK. Lancet Respir Med. 2021;9(7):699-711.

11. Schultze A, Walker AJ, MacKenna B, et al. Inhaled corticosteroid use and risk COVID-19 related death among 966,461 patients with COPD or asthma: an OpenSAFELY analysis. medRxiv. 2020:2020.2006.2019.20135491-20132020.20135406.20135419.20135491.

12. Zhu Z, Hasegawa K, Ma B, Fujiogi M, Camargo CA, Jr., Liang L. Association of asthma and its genetic predisposition with the risk of severe COVID-19. J Allergy Clin Immunol. 2020;146(2):327-329.e324.

13. Yang JM, Koh HY, Moon SY, et al. Allergic disorders and susceptibility to and severity of COVID-19: A nationwide cohort study. J Allergy Clin Immunol. 2020;146(4):790-798.

14. Wolf A, Dedman D, Campbell J, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. Int J Epidemiol. 2019;48(6):1740-1740g.

15. NHS Digital. https://digital.nhs.uk/about-nhs-digital/corporate-information-and-documents/directions-and-data-provision-notices/data-provision-notices-dpns/sgss-and-chess-data. Published 2021. Accessed 2021.

16. Office of National Statistics. Coronavirus (COVID-19) Infection Survey technical article: waves and lags of COVID-19 in England, June 2021. 2021.
17. Nissen F, Morales DR, Mullerova H, Smeeth L, Douglas IJ, Quint JK. Validation of asthma recording in the Clinical Practice Research Datalink (CPRD). *BMJ Open*. 2017;7(8):e017474-e017474.

18. Bloom CI, Palmer T, Feary J, Quint JK, Cullinan P. Exacerbation Patterns in Adults with Asthma in England. A Population-based Study. *Am J Respir Crit Care Med*. 2019;199(4):446-453.

19. Bloom CI, Nissen F, Douglas IJ, Smeeth L, Cullinan P, Quint JK. Exacerbation risk and characterisation of the UK’s asthma population from infants to old age. *Thorax*. 2018;73(4):313-320.

20. Bhaskaran K, Smeeth L. What is the difference between missing completely at random and missing at random? *Int J Epidemiol*. 2014;43(4):1336-1339.

21. Bloom CI, Wong E, Hickman K, Elkin S. Influence of the first wave of COVID-19 on asthma inhaler prescriptions. *NPJ Prim Care Respir Med (In Press)*. 2021.

22. Terry PD, Heidel RE, Dhand R. Asthma in Adult Patients with COVID-19. Prevalence and Risk of Severe Disease. *Am J Respir Crit Care Med*. 2021;203(7):893-905.

23. Bhaskaran K, Bacon S, Evans SJ, et al. Factors associated with deaths due to COVID-19 versus other causes: population-based cohort analysis of UK primary care data and linked national death registrations within the OpenSAFELY platform. *Lancet Reg Health Eur*. 2021;6:100109.

24. Lee SW, Kim SY, Moon SY, et al. Estimating COVID-19 Infection and Severity Risks in Patients with Chronic Rhinosinusitis: A Korean Nationwide Cohort Study. *J Allergy Clin Immunol Pract*. 2021;9(6):2262-2271.e2262.
Figure legends

Figure 1. Flow diagram of inclusion and exclusion criteria

Figure 2. Comparing forest plots of the associations between asthma phenotype and each COVID-19 outcome, after adjusting for all other risk factors (see Figure S7 for forest plot including all variables and Tables S3, S5-6 for unadjusted and adjusted effect estimates).

Figure 3. Comparing forest plots of the associations between asthma phenotype and hospitalisation for the three different respiratory infections, COVID-19, influenza, and pneumonia, after adjusting for all other risk factors (ethnicity, socioeconomic deprivation, obesity, atopy, cardiac disease, diabetes, CVA, CRF, dementia, cancer).

Figure 4. Association between maximum absolute blood eosinophil count and ICU admission or death in the asthma patients. Model was adjusted for sex, age, ethnicity, socioeconomic deprivation, obesity, atopy, cardiac disease, diabetes, CVA, CRF, dementia and cancer. The solid black line represents the adjusted hazard ratio for the outcome (ICU admission/death) for the continuous variable of maximum absolute blood eosinophil count. The dotted black lines represent the 95% confidence interval of the hazard ratio.
Table 1. Characteristics of the asthma cohort.

|                                | General Population | Asthma       | Total         |
|--------------------------------|--------------------|--------------|---------------|
|                                | 748,327            | 434,348      | 1,182,675     |
| **GP-diagnosis (COVID-19)**    |                    |              |               |
| No                             | 741,545 (99.1%)    | 426,292 (98.1%) | 1,167,837 (98.7%) |
| Yes                            | 6,782 (0.9%)       | 8,056 (1.9%) | 14,838 (1.3%) |
| **Hospital admissions (COVID-19)** |                    |              |               |
| No                             | 747,348 (99.9%)    | 433,358 (99.8%) | 1,180,706 (99.8%) |
| Yes                            | 979 (0.1%)         | 990 (0.2%) | 1,969 (0.2%) |
| **Death/ICU (COVID-19)**      |                    |              |               |
| No                             | 747,936 (99.9%)    | 433,990 (99.9%) | 1,181,926 (99.9%) |
| Yes                            | 391 (0.1%)         | 358 (0.1%) | 749 (0.1%) |
| **Age**                        | median=48.5 (IQR 34.5-61.5) | median=49.5 (IQR 35.5-62.5) | median=48.5 (IQR 35.5-61.5) |
| **Sex**                        |                    |              |               |
| Male                           | 319,577 (42.7%)    | 182,476 (42.0%) | 502,053 (42.5%) |
| Female                         | 428,750 (57.3%)    | 251,872 (58.0%) | 680,622 (57.5%) |
| **Ethnicity**                  |                    |              |               |
| White                          | 423,960 (56.7%)    | 289,872 (66.7%) | 713,832 (60.4%) |
| Asian                          | 39,688 (5.3%)      | 28,078 (6.5%) | 67,766 (5.7%) |
| Black                          | 16,776 (2.2%)      | 11,237 (2.6%) | 28,013 (2.4%) |
| Unknown                        | 267,903 (35.8%)    | 105,161 (24.2%) | 373,064 (31.5%) |
| **Socioeconomic deprivation (IMD)** |                    |              |               |
| 1                              | 175,451 (23.4%)    | 97,810 (22.5%) | 273,261 (23.1%) |
| 2                              | 154,484 (20.6%)    | 88,318 (20.3%) | 242,802 (20.5%) |
| 3                              | 144,689 (19.3%)    | 83,284 (19.2%) | 227,973 (19.3%) |
| 4                              | 143,182 (19.1%)    | 84,305 (19.4%) | 227,487 (19.2%) |
| 5 (most deprived)              | 129,909 (17.4%)    | 80,150 (18.5%) | 210,059 (17.8%) |
| Missing                        | 612 (0.1%)         | 481 (0.1%) | 1,093 (0.1%) |
| **Asthma severity**            |                    |              |               |
| No asthma                      | 748,327 (100.0%)   | 0 (0.0%)     | 748,327 (63.3%) |
| SABA only                      | Not applicable     | 133,612 (30.8%) | 133,612 (11.3%) |
| Intermittent ICS (1-3 in baseline year) | Not applicable | 62,172 (14.3%) | 62,172 (5.3%) |
| Treatment Category                                      | Not applicable | Count (Percentage) |
|-------------------------------------------------------|----------------|-------------------|
| Regular ICS (≥4 in baseline year)                      |                | 57061 (13.1%)     |
| Intermittent (ICS + add-on 1-3 in baseline year)       |                | 44118 (10.2%)     |
| Regular ICS + add-on (≥4 in baseline year)             |                | 137385 (31.6%)    |

| Exacerbations                                           |                | Count (Percentage) |
|-------------------------------------------------------|----------------|-------------------|
| None                                                   |                | 748327 (100.0%)  |
| 1 GP managed in past year                              |                | 50951 (11.7%)     |
| >1 GP managed or ≥1 hospital admission in 5 years      |                | 32631 (7.5%)      |

| Comorbidities                                          |                | Count (Percentage) |
|-------------------------------------------------------|----------------|-------------------|
| Atopy                                                  |                |                   |
| No                                                    | 532142 (71.1%) | 182046 (41.9%)    |
| Yes                                                   | 216185 (28.9%) | 252302 (58.1%)    |
| Obesity                                                |                |                   |
| No                                                    | 607562 (81.2%) | 305657 (70.4%)    |
| Yes                                                   | 140765 (18.8%) | 128691 (29.6%)    |
| Cardiac disease                                        |                |                   |
| No                                                    | 580109 (77.5%) | 309664 (71.3%)    |
| Yes                                                   | 168218 (22.5%) | 124684 (28.7%)    |
| Diabetes                                               |                |                   |
| No                                                    | 502529 (67.2%) | 262321 (60.4%)    |
| Yes                                                   | 245798 (32.8%) | 172027 (39.6%)    |
| Dementia                                               |                |                   |
| No                                                    | 708817 (94.7%) | 410548 (94.5%)    |
| Yes                                                   | 39510 (5.3%)   | 23800 (5.5%)      |
| Cerebrovascular disease                                |                |                   |
| No                                                    | 741071 (99.0%) | 429049 (98.8%)    |
| Yes                                                   | 7256 (1.0%)    | 5299 (1.2%)       |
| Chronic renal failure                                  |                |                   |
| No                                                    | 728907 (97.4%) | 420029 (96.7%)    |
| Yes                                                   | 19420 (2.6%)   | 14319 (3.3%)      |
| Cancer                                                 |                |                   |
| No                                                    | 705792 (94.3%) | 407426 (93.8%)    |
| Yes                                                   | 42535 (5.7%)   | 26922 (6.2%)      |
Table 2. Rates of hospitalisation in the asthma cohort for each respiratory infection, by time period.

| Time period               | Admission  | Number of events |Rates per 100,000 (95% CI) |
|---------------------------|------------|------------------|---------------------------|
|                           |            | Asthma | General population | Total       | Asthma                  | General population |
| 1st Feb - 26th June 2020 | COVID-19   | 990    | 979               | 1,969       | 19.33                   | 11.08               |
|                           | Influenza  | 211    | 124               | 335         | 3.99                    | 1.37                |
| 1st Feb - 26th June 2019 | Pneumonia  | 373    | 245               | 618         | 7.06                    | 2.71                |
| 1st Dec 2018 - 26th April 2019 | Influenza | 369    | 225               | 594         | 6.99                    | 2.49                |
Figure 1: Flow diagram of inclusion and exclusion criteria

476x377mm (130 x 130 DPI)
Figure 2: Comparing forest plots of the associations between asthma phenotype and each COVID-19 outcome, after adjusting for all other risk factors (see Figure S7 for forest plot including all variables and Tables S3, S5-6 for unadjusted and adjusted effect estimates).
Figure 3: Comparing forest plots of the associations between asthma phenotype and hospitalisation for the three different respiratory infections, COVID-19, influenza, and pneumonia, after adjusting for all other risk factors (ethnicity, socioeconomic deprivation, obesity, atopy, cardiac disease, diabetes, CVA, CRF, dementia, cancer).

429x312mm (38 x 38 DPI)
Figure 4: Association between maximum absolute blood eosinophil count and ICU admission or death in the asthma patients. Model was adjusted for sex, age, ethnicity, socioeconomic deprivation, obesity, atopy, cardiac disease, diabetes, CVA, CRF, dementia and cancer. The solid black line represents the adjusted hazard ratio for the outcome (ICU admission/death) for the continuous variable of maximum absolute blood eosinophil count. The dotted black lines represent the 95% confidence interval of the hazard ratio.
### Online Data Supplement

|                          | General Population | Allergic rhinitis | Total       |
|--------------------------|--------------------|-------------------|-------------|
| **Total**                | 115,357            | 41,890            | 157,247     |

#### GP-diagnosis (COVID-19)
- **No**
  - Total 114,396 (99.17%)
  - Allergic rhinitis 41,076 (98.06%)
  - Total 155,472 (98.87%)
- **Yes**
  - Total 961 (0.83%)
  - Allergic rhinitis 814 (1.94%)
  - Total 1,775 (1.13%)

#### Hospital admissions (COVID-19)
- **No**
  - Total 115,205 (99.87%)
  - Allergic rhinitis 41,827 (99.85%)
  - Total 157,032 (99.86%)
- **Yes**
  - Total 1,52 (0.13%)
  - Allergic rhinitis 63 (0.15%)
  - Total 215 (0.14%)

#### ICU/death (COVID-19)
- **No**
  - Total 115,302 (99.95%)
  - Allergic rhinitis 41,876 (99.97%)
  - Total 157,178 (99.96%)
- **Yes**
  - Total 55 (0.05%)
  - Allergic rhinitis 14 (0.03%)
  - Total 69 (0.04%)

#### Age
- Median=49.5 (IQR 34.5-63.5)
- Median=44.5 (IQR 31.5-59.5)
- Median=48.5 (IQR 33.5-62.5)

#### Sex
- Male
  - Total 47,084 (40.82%)
  - Allergic rhinitis 17,148 (40.94%)
  - Total 64,232 (40.85%)
- Female
  - Total 68,273 (59.18%)
  - Allergic rhinitis 24,742 (59.06%)
  - Total 93,015 (59.15%)

#### Ethnicity
- White
  - Total 63,026 (54.64%)
  - Allergic rhinitis 26,538 (63.35%)
  - Total 89,564 (56.96%)
- Asian
  - Total 6,089 (5.28%)
  - Allergic rhinitis 3,931 (9.38%)
  - Total 10,020 (6.37%)
- Black
  - Total 2,613 (2.27%)
  - Allergic rhinitis 1,786 (4.26%)
  - Total 4,399 (2.80%)
- Unknown
  - Total 43,629 (37.82%)
  - Allergic rhinitis 9,635 (23.00%)
  - Total 53,264 (33.87%)

#### Socioeconomic deprivation (IMD)
- 1
  - Total 26,174 (22.69%)
  - Allergic rhinitis 10,275 (24.53%)
  - Total 36,449 (23.18%)
- 2
  - Total 23,246 (20.15%)
  - Allergic rhinitis 8,653 (20.66%)
  - Total 31,899 (20.29%)
- 3
  - Total 22,537 (19.54%)
  - Allergic rhinitis 7,978 (19.05%)
  - Total 30,515 (19.41%)
- 4
  - Total 22,862 (19.82%)
  - Allergic rhinitis 7,979 (19.05%)
  - Total 30,841 (19.61%)
- 5 (most deprived)
  - Total 20,441 (17.72%)
  - Allergic rhinitis 6,977 (16.66%)
  - Total 27,418 (17.44%)
- Missing
  - Total 97 (0.08%)
  - Allergic rhinitis 28 (0.07%)
  - Total 125 (0.08%)

#### Comorbidities

| Condition                 | General Population | Allergic rhinitis | Total       |
|---------------------------|--------------------|-------------------|-------------|
| Obesity                   | 94,720 (82.11%)    | 30,930 (73.84%)   | 125,650 (79.91%) |
| Yes                       | 20,637 (17.89%)    | 10,960 (26.16%)   | 31,597 (20.09%) |
| Cardiac disease           | 88,538 (76.75%)    | 31,550 (75.32%)   | 120,088 (76.37%) |
| Yes                       | 26,819 (23.25%)    | 10,340 (24.68%)   | 37,159 (23.63%) |
| Diabetes                  | 77,433 (67.12%)    | 25,586 (61.08%)   | 103,019 (65.51%) |
| Yes                       | 37,924 (32.88%)    | 16,304 (38.92%)   | 54,228 (34.49%) |
| Dementia                  | 109,151 (94.62%)   | 39,824 (95.07%)   | 148,975 (94.74%) |
| Yes                       | 6,206 (5.38%)      | 2,066 (4.93%)     | 8,272 (5.26%)   |
| Cerebrovascular disease   | 114,245 (99.04%)   | 41,533 (99.15%)   | 155,778 (99.07%) |
| Yes                       | 1112 (0.96%)       | 357 (0.85%)       | 1469 (0.93%)    |
| Chronic renal failure     | 112,200 (97.26%)   | 40,818 (97.44%)   | 153,018 (97.31%) |
| Yes                       | 3,157 (2.74%)      | 1,072 (2.56%)     | 4,229 (2.69%)   |
| Cancer                    | 102,842 (89.15%)   | 37,458 (89.42%)   | 140,300 (89.22%) |
| Yes                       | 12,515 (10.85%)    | 4,432 (10.58%)    | 16,947 (10.78%) |

Table S1. Characteristics of the allergic rhinitis cohort.
|                          | Hospital admission |
|--------------------------|--------------------|
|                          | No                  | Yes                 |
| **TOTAL**                | 151 (100.0%)       | 502 (100.0%)       |
| **Exposure**             |                    |                    |
| General Population       | 97 (64.2%)         | 250 (49.8%)        |
| Asthma                   | 54 (35.8%)         | 252 (50.2%)        |
| **GP-diagnosis**         |                    |                    |
| Suspected                | 42 (27.8%)         | 59 (11.8%)         |
| Confirmed                | 57 (37.7%)         | 230 (45.8%)        |
| None                     | 52 (34.4%)         | 213 (42.4%)        |
| **Hospital admissions (COVID-19)** |                |                    |
| No                       | 151 (100.0%)       | 0 (0.0%)           |
| Yes                      | 0 (0.0%)           | 502 (100.0%)       |
| **ICU/death (COVID-19)** |                    |                    |
| Yes                      | 151 (100.0%)       | 502 (100.0%)       |
| **Age**                  |                    |                    |
| Age category (years)     |                    |                    |
| 18-39                    | 1 (0.7%)           | 2 (0.4%)           |
| 40-49                    | 4 (2.6%)           | 8 (1.6%)           |
| 50-59                    | 13 (8.6%)          | 41 (8.2%)          |
| 60-69                    | 18 (11.9%)         | 77 (15.3%)         |
| 70-79                    | 35 (23.2%)         | 154 (30.7%)        |
| 80+                      | 80 (53.0%)         | 220 (43.8%)        |
| **Sex**                  |                    |                    |
| Male                     | 64 (42.4%)         | 240 (47.8%)        |
| Female                   | 87 (57.6%)         | 262 (52.2%)        |
| **Ethnicity**            |                    |                    |
| White                    | 101 (66.9%)        | 349 (69.5%)        |
| Asian                    | 15 (9.9%)          | 60 (12.0%)         |
| Black                    | 10 (6.6%)          | 34 (6.8%)          |
| Unknown                  | 25 (16.6%)         | 59 (11.8%)         |
| **Socioeconomic status (IMD)** |                |                    |
| 1                        | 30 (19.9%)         | 78 (15.5%)         |
| 2                        | 35 (23.2%)         | 94 (18.7%)         |
| 3                        | 25 (16.6%)         | 112 (22.3%)        |
| 4                        | 32 (21.2%)         | 118 (23.5%)        |
| 5 (most deprived)        | 29 (19.2%)         | 100 (19.9%)        |
| **Asthma severity**      |                    |                    |
| Asthma                   | 97 (64.2%)         | 250 (49.8%)        |
| No asthma                | 97 (64.2%)         | 318 (63.3%)        |
| SABA only                | 13 (8.6%)          | 41 (8.2%)          |
| ICS only                 | 12 (7.9%)          | 65 (12.9%)         |
| ICS + add-on             | 29 (19.2%)         | 146 (29.1%)        |
| **Exacerbations**        |                    |                    |
| None                     | 141 (93.4%)        | 418 (83.3%)        |
| 1 GP managed in past year| 6 (4.0%)           | 26 (5.2%)          |
| >1 GP managed or ≥1 hospital admission in 5 years | 4 (2.6%) | 58 (11.6%) |
| **Comorbidities**        |                    |                    |
| Atopy                    | 97 (64.2%)         | 318 (63.3%)        |
| Yes                      | 54 (35.8%)         | 184 (36.7%)        |
| Obesity                  |                    |                    |
| Condition                        | No                  | Yes                  |
|---------------------------------|---------------------|----------------------|
| Cardiac disease                 |                     |                      |
| **No**                          | 126 (83.4%)         | 320 (63.7%)          |
| **Yes**                         | 25 (16.6%)          | 182 (36.3%)          |
| Diabetes                        |                     |                      |
| **No**                          | 75 (49.7%)          | 175 (34.9%)          |
| **Yes**                         | 76 (50.3%)          | 327 (65.1%)          |
| Dementia                        |                     |                      |
| **No**                          | 74 (49.0%)          | 388 (77.3%)          |
| **Yes**                         | 77 (51.0%)          | 114 (22.7%)          |
| Cerebrovascular disease         |                     |                      |
| **No**                          | 134 (88.7%)         | 461 (91.8%)          |
| **Yes**                         | 17 (11.3%)          | 41 (8.2%)            |
| Chronic renal failure           |                     |                      |
| **No**                          | 119 (78.8%)         | 400 (79.7%)          |
| **Yes**                         | 32 (21.2%)          | 102 (20.3%)          |
| Cancer                          |                     |                      |
| **No**                          | 128 (84.8%)         | 391 (77.9%)          |
| **Yes**                         | 23 (15.2%)          | 111 (22.1%)          |

Table S2. Characteristics of asthma cohort that died, grouped by whether they were admitted to hospital prior to their death from COVID-19 (including any hospital admission, even if not admitted for COVID-19).
|                      | Unadjusted |          |          | Adjusted |          |          |
|----------------------|------------|----------|----------|----------|----------|----------|
|                      | HR         | p-value  | 95% CI   | HR       | p-value  | 95% CI   |
| **Asthma**           |            |          |          |          |          |          |
| No asthma            | Reference  |          |          | Reference|          |          |
| SABA only            | 1.92       | <0.001   | 1.81-2.05| 1.63     | <0.001   | 1.53-1.74|
| Intermittent ICS     | 1.66       | <0.001   | 1.51-1.81| 1.42     | <0.001   | 1.29-1.56|
| Regular ICS          | 1.78       | <0.001   | 1.62-1.95| 1.41     | <0.001   | 1.28-1.55|
| Intermittent ICS + add-on | 2.30 | <0.001   | 2.08-2.55| 1.79     | <0.001   | 1.61-1.99|
| Regular ICS + add-on | 2.35       | <0.001   | 2.22-2.48| 1.73     | <0.001   | 1.62-1.85|
| **Exacerbations (year prior)** | |          |          |          |          |          |
| 0                    | Reference  |          |          | Reference|          |          |
| 1                    | 2.65       | <0.001   | 2.42-2.89| 1.43     | <0.001   | 1.29-1.58|
| >2 GP/≥1 Hospital in 5 yrs | 3.51 | <0.001   | 3.16-3.89| 1.76     | <0.001   | 1.57-1.97|
| **Ethnicity**        |            |          |          |          |          |          |
| White                | Reference  |          |          | Reference|          |          |
| Asian                | 1.35       | <0.001   | 1.23-1.47| 1.37     | <0.001   | 1.25-1.51|
| Black                | 1.41       | <0.001   | 1.25-1.60| 1.40     | <0.001   | 1.23-1.59|
| Unknown              | 0.47       | <0.001   | 0.45-0.50| 0.59     | <0.001   | 0.55-0.63|
| **Socioeconomic status (IMD)** | |          |          |          |          |          |
| 1                    | Reference  |          |          | Reference|          |          |
| 2                    | 1.09       | <0.05    | 1.01-1.17| 1.05     | 0.22     | 0.97-1.13|
| 3                    | 1.19       | <0.001   | 1.10-1.28| 1.11     | <0.05    | 1.02-1.20|
| 4                    | 1.36       | <0.001   | 1.26-1.48| 1.23     | <0.001   | 1.13-1.33|
| 5 (most deprived)    | 1.49       | <0.001   | 1.37-1.63| 1.28     | <0.001   | 1.16-1.40|
| **Atopy**            | 1.51       | <0.001   | 1.44-1.57| 1.09     | <0.001   | 1.04-1.14|
| **Obesity**          | 1.64       | <0.001   | 1.56-1.71| 1.29     | <0.001   | 1.22-1.35|
| **Cardiac disease**  | 1.45       | <0.001   | 1.37-1.53| 1.16     | <0.001   | 1.09-1.23|
| **Diabetes**         | 1.47       | <0.001   | 1.41-1.54| 1.22     | <0.001   | 1.16-1.29|
| **Dementia**         | 1.31       | <0.001   | 1.20-1.43| 1.40     | <0.001   | 1.27-1.53|
| **CVA**              | 1.86       | <0.001   | 1.59-2.17| 1.59     | <0.001   | 1.34-1.88|
| **CRF**              | 1.55       | <0.001   | 1.39-1.73| 1.27     | <0.001   | 1.13-1.43|
| **Cancer**           | 1.15       | <0.001   | 1.07-1.25| 1.15     | <0.001   | 1.06-1.25|

Table S3. Univariable and multivariable regression estimates for GP-diagnosis of COVID-19 in the asthma cohort. Analysed using a stratified Cox model for the matched patients (matched on age, gender and GP practice). HR= hazard ratio, CI = confidence interval, ICS = Inhaled corticosteroids, GP = general practitioner, CVA = cerebrovascular accident, CRF = chronic renal failure.
|                              | Unadjusted |          |          |          | Adjusted |          |          |          |
|------------------------------|------------|----------|----------|----------|----------|----------|----------|----------|
|                              | HR         | p-value  | 95% CI   | HR       | p-value  | 95% CI   | HR       | p-value  | 95% CI   |
| Asthma                       |            |          |          |          |          |          |          |          |          |
| No asthma                    | Reference  |          |          | Reference |          |          |          |          |          |
| SABA only                    | 1.15       | 0.18     | 0.94-1.42| 0.94     | 0.56     | 0.75-1.17|          |          |          |
| Intermittent ICS             | 1.06       | 0.67     | 0.81-1.40| 0.90     | 0.49     | 0.67-1.21|          |          |          |
| Regular ICS                  | 1.52       | <0.001   | 1.23-1.89| 1.27     | <0.05    | 1.01-1.61|          |          |          |
| Intermittent ICS + add-on    | 2.47       | <0.001   | 1.82-3.35| 2.00     | <0.001   | 1.43-2.79|          |          |          |
| Regular ICS + add-on         | 2.17       | <0.001   | 1.89-2.50| 1.63     | <0.001   | 1.37-1.94|          |          |          |
| Exacerbations (year prior)   |            |          |          |          |          |          |          |          |          |
| 0                            | Reference  |          |          | Reference |          |          |          |          |          |
| 1                            | 1.96       | <0.001   | 1.53-2.52| 1.20     | 0.22     | 0.90-1.61|          |          |          |
| >2 GP/≥1 hospital in 5 yrs   | 3.34       | <0.001   | 2.58-4.33| 1.82     | <0.001   | 1.34-2.47|          |          |          |
| Ethnicity                    |            |          |          |          |          |          |          |          |          |
| White                        | Reference  |          |          | Reference |          |          |          |          |          |
| Asian                        | 1.64       | <0.001   | 1.31-2.07| 1.54     | <0.01    | 1.21-1.96|          |          |          |
| Black                        | 2.10       | <0.001   | 1.57-2.80| 1.91     | <0.001   | 1.40-2.61|          |          |          |
| Unknown                      | 0.39       | <0.001   | 0.32-0.47| 0.49     | <0.001   | 0.40-0.60|          |          |          |
| Socioeconomic status (IMD)   |            |          |          |          |          |          |          |          |          |
| 1                            | Reference  |          |          | Reference |          |          |          |          |          |
| 2                            | 1.31       | 0.01     | 1.07-1.61| 1.29     | 0.02     | 1.04-1.61|          |          |          |
| 3                            | 1.49       | <0.001   | 1.20-1.85| 1.46     | <0.01    | 1.16-1.83|          |          |          |
| 4                            | 1.64       | <0.001   | 1.31-2.06| 1.44     | <0.01    | 1.12-1.84|          |          |          |
| 5 (most deprived)            | 1.95       | <0.001   | 1.53-2.50| 1.61     | <0.01    | 1.23-2.11|          |          |          |
| Atopy                        | 1.27       | <0.001   | 1.13-1.42| 0.97     | 0.70     | 0.85-1.11|          |          |          |
| Obesity                      | 1.86       | <0.001   | 1.64-2.15| 1.49     | <0.001   | 1.30-1.72|          |          |          |
| Cardiac disease              | 1.91       | <0.001   | 1.66-2.20| 1.47     | <0.001   | 1.26-1.73|          |          |          |
| Diabetes                     | 1.75       | <0.001   | 1.54-1.98| 1.33     | <0.001   | 1.16-1.53|          |          |          |
| Dementia                     | 1.65       | <0.001   | 1.36-2.01| 1.84     | <0.001   | 1.49-2.27|          |          |          |
| CVA                          | 2.21       | <0.001   | 1.68-2.92| 1.72     | <0.001   | 1.28-2.32|          |          |          |
| CRF                          | 1.95       | <0.001   | 1.60-2.37| 1.67     | <0.001   | 1.34-2.06|          |          |          |
| Cancer                       | 1.33       | <0.01    | 1.13-1.58| 1.32     | <0.01    | 1.10-1.59|          |          |          |

Table S4. Univariable and multivariable regression estimates for COVID-19 hospital admission in the asthma cohort. Analysed using a stratified Cox models for the matched patients (matched on age, gender and GP practice). HR= hazard ratio, CI = confidence interval, ICS = Inhaled corticosteroids, GP = general practitioner, CVA = cerebrovascular accident, CRF = chronic renal failure.
|                                | Unadjusted |                | Adjusted       |                |
|--------------------------------|------------|----------------|----------------|----------------|
|                                | HR         | p-value        | 95% CI         | HR             | p-value        | 95% CI         |
| **Asthma**                     |            |                |                |                |                |                |
| No asthma                      | Reference  |                | Reference      |                |                |                |
| SABA only                      | 1.23       | 0.24           | 0.87-1.73      | 1.03           | 0.87           | 0.70-1.52      |
| Intermittent ICS               | 0.94       | 0.80           | 0.57-1.54      | 0.97           | 0.91           | 0.56-1.68      |
| Regular ICS                    | 1.15       | 0.41           | 0.83-1.59      | 1.10           | 0.62           | 0.76-1.60      |
| Intermittent ICS + add-on      | 1.11       | 0.72           | 0.62-2.01      | 0.87           | 0.68           | 0.46-1.66      |
| Regular ICS + add-on           | 1.96       | <0.001         | 1.57-2.45      | 1.70           | <0.001         | 1.27-2.26      |
| **Exacerbations (year prior)** |            |                |                |                |                |                |
| 0                              | Reference  |                | Reference      |                |                |                |
| 1                              | 1.15       | 0.51           | 0.76-1.72      | 0.73           | 0.21           | 0.44-1.20      |
| >2 GP/≥1 hospital in 5 yrs     | 2.39       | <0.001         | 1.61-3.55      | 1.66           | 0.04           | 1.03-2.68      |
| **Ethnicity**                  |            |                |                |                |                |                |
| White                          | Reference  |                | Reference      |                |                |                |
| Asian                          | 2.35       | <0.001         | 1.57-3.53      | 2.15           | <0.001         | 1.39-3.35      |
| Black                          | 3.13       | <0.001         | 1.84-5.32      | 2.62           | <0.001         | 1.48-4.63      |
| Unknown                        | 0.38       | <0.001         | 0.27-0.54      | 0.48           | <0.001         | 0.33-0.70      |
| **Socioeconomic status (IMD)** |            |                |                |                |                |                |
| 1                              | Reference  |                | Reference      |                |                |                |
| 2                              | 1.56       | 0.01           | 1.11-2.18      | 1.60           | 0.01           | 1.10-2.33      |
| 3                              | 1.94       | <0.001         | 1.36-2.77      | 1.89           | <0.001         | 1.28-2.79      |
| 4                              | 2.22       | <0.001         | 1.52-3.25      | 2.04           | <0.001         | 1.34-3.09      |
| 5 (most deprived)              | 2.14       | <0.001         | 1.41-3.25      | 1.73           | 0.02           | 1.09-2.72      |
| **Atopy**                      |            |                |                |                |                |                |
|                               | 1.08       | 0.45           | 0.89-1.30      | 0.89           | 0.31           | 0.71-1.11      |
| **Obesity**                    |            |                |                |                |                |                |
|                               | 1.61       | <0.001         | 1.31-1.99      | 1.39           | 0.01           | 1.09-1.78      |
| **Cardiac disease**            |            |                |                |                |                |                |
|                               | 1.70       | <0.001         | 1.35-2.14      | 1.36           | 0.02           | 1.05-1.78      |
| **Diabetes**                   |            |                |                |                |                |                |
|                               | 1.82       | <0.001         | 1.47-2.24      | 1.38           | 0.01           | 1.09-1.75      |
| **Dementia**                   |            |                |                |                |                |                |
|                               | 2.94       | <0.001         | 2.24-3.87      | 3.32           | <0.001         | 2.46-4.47      |
| **CVA**                        |            |                |                |                |                |                |
|                               | 1.98       | <0.001         | 1.33-2.95      | 1.74           | 0.01           | 1.12-2.71      |
| **CRF**                        |            |                |                |                |                |                |
|                               | 1.67       | <0.001         | 1.27-2.19      | 1.55           | 0.01           | 1.14-2.12      |
| **Cancer**                     |            |                |                |                |                |                |
|                               | 1.15       | 0.31           | 0.88-1.49      | 1.21           | 0.20           | 0.90-1.62      |

Table S5. Univariable and multivariable regression estimates for COVID-19 ICU admission or death in the asthma cohort. Analysed using a stratified Cox models for the matched patients (matched on age, gender and GP practice). HR= hazard ratio, CI = confidence interval, ICS = Inhaled corticosteroids, GP = general practitioner, CVA = cerebrovascular accident, CRF = chronic renal failure.
### Asthma patients included in the eosinophil analysis

|                                | Asthma patients included in the eosinophil analysis | All asthma patients in the asthma cohort |
|--------------------------------|----------------------------------------------------|------------------------------------------|
| **TOTAL**                      | 290639 (66.9%)                                     | 434348 (100.0%)                          |
| Hospital admissions (COVID-19) |                                                    |                                          |
| No                             | 290010 (99.8%)                                     | 433358 (99.8%)                           |
| Yes                            | 629 (0.2%)                                         | 990 (0.2%)                               |
| Death/ICU (COVID-19)           |                                                    |                                          |
| No                             | 290449 (99.9%)                                     | 433990 (99.9%)                           |
| Yes                            | 190 (0.1%)                                         | 358 (0.1%)                               |

### Demographics

| **Age** | Median=51.5 (IQR 38.5-62.5) | Median=49.5 (IQR 35.5-62.5) |
|---------|------------------------------|------------------------------|
| **Sex** | Male 106472 (36.6%)          | 182476 (42.0%)               |
|         | Female 184167 (63.4%)        | 251872 (58.0%)               |
| **Ethnicity** |                                 |                              |
| White   | 203598 (70.1%)               | 289872 (66.7%)               |
| Asian   | 21060 (7.2%)                 | 28078 (6.5%)                 |
| Black   | 8113 (2.8%)                  | 11237 (2.6%)                 |
| Unknown | 57868 (19.9%)                | 105161 (24.2%)               |
| **Socioeconomic deprivation (IMD)** |                                 |                              |
| 1       | 62662 (21.6%)                | 97810 (22.5%)                |
| 2       | 58058 (20.0%)                | 88318 (20.3%)                |
| 3       | 55619 (19.1%)                | 83284 (19.2%)                |
| 4       | 57686 (19.8%)                | 84305 (19.4%)                |
| 5 (most deprived) | 56285 (19.4%) | 80150 (18.5%)               |
| Missing | 329 (0.1%)                   | 481 (0.1%)                   |
| **Asthma severity** |                                 |                              |
| Asthma  | SABA only 84355 (29.0%)      | 133612 (30.8%)               |
|         | ICS 1-3/year 40526 (13.9%)   | 62172 (14.3%)                |
|         | ICS ≥4/year 39060 (13.4%)    | 57061 (13.1%)                |
|         | ICS + add-on 1-3/year 29451 (10.1%) | 44118 (10.2%) |
|         | ICS + add-on ≥4/year 97247 (33.5%) | 137385 (31.6%) |
| **Exacerbations** |                                 |                              |
| None    | 231079 (79.2%)               | 350766 (80.8%)               |
| 1 GP managed in past year    | 37094 (12.7%)                 | 50951 (11.7%)                 |
| >1 GP managed or ≥1 hospital admission in 5 years | 23520 (8.1%) | 32631 (7.5%) |
| **Comorbidities** |                                 |                              |
| Obesity | No 194014 (66.8%)            | 305657 (70.4%)               |
|         | Yes 96625 (33.2%)            | 128691 (29.6%)               |
| Cardiac disease |                                 |                              |
| No      | 196976 (67.8%)               | 309664 (71.3%)               |
| Yes     | 93663 (32.2%)                | 124684 (28.7%)               |
| Diabetes | No 161190 (55.5%)           | 262321 (60.4%)               |
|         | Yes 129449 (44.5%)          | 172027 (39.6%)               |
| Dementia | No 273529 (94.1%)           | 410548 (94.5%)               |
|                          | Yes                  | No                  |
|--------------------------|----------------------|---------------------|
| Cerebrovascular disease  | 17110 (5.9%)         | 23800 (5.5%)        |
|                         | 3471 (1.2%)          | 5299 (1.2%)         |
| Chronic renal failure    | 281633 (96.9%)       | 420029 (96.7%)      |
|                         | 9006 (3.1%)          | 14319 (3.3%)        |

Table S6. Characteristics of asthma cohort that were included in the eosinophil analysis as compared to the whole asthma population in the asthma cohort.
Figure S1: Distribution over time, between 1st February 2020 and 26th June 2020, of GP diagnoses of suspected or confirmed COVID-19, grouped by exposure in the asthma cohort.
Figure S2: Distribution over time, between 1st February 2020 and 26th June 2020, of COVID-19 hospital admissions, grouped by exposure in the asthma cohort.
Figure S3: Distribution over time, between 1st February 2020 and 26th June 2020, of COVID-19 deaths in the asthma cohort.

403x280mm (38 x 38 DPI)
Figure S4: Kaplan-Meier of the whole asthma cohort, time to (A) GP-diagnosis, (B) Hospital admission, (C) ICU admission or death. Note each KM has a different scale for the y-axis.

270x565mm (130 x 130 DPI)
Figure S5: All model covariates shown in the forest plot for each of the three Cox models, varying by outcome: GP diagnosis of COVID-19, hospitalised for COVID-19 and admitted to ICU or death due to COVID-19, in the asthma cohort. Analysed using stratified Cox models for the matched patients (matched on age, gender, and GP practice).

411x300mm (38 x 38 DPI)
Figure S6: Association between variables and having a GP consultation for COVID-19 advice or to report COVID-19 exposure in the asthma cohort. Analysed using a stratified Cox model for the matched patients (matched on age, gender and GP practice).

405x279mm (236 x 236 DPI)
Figure S7: Association between variables, and a suspected COVID-19 diagnosis becoming a confirmed COVID-19 diagnosis, in the asthma cohort. Analysed using mixed-effects logistic regression model (GP practice as a random effect).

402x301mm (236 x 236 DPI)
Figure S8: Sensitivity analysis to measure the association between variables and having a confirmed COVID-19 code as a GP diagnosis in the asthma cohort. Analysed using a stratified Cox model for the matched patients (matched on age, gender and GP practice).
Figure S9: Sensitivity analysis, only including death as the last COVID-19 outcome (excluding ICU admission), stratified Cox model on matched patients (matched on age, gender, and GP practice) and adjusted for all covariates as before (ethnicity, IMD, obesity, cardiac disease, diabetes, CRF, CVA and cancer) but only the asthma phenotypes are shown here.
Figure S10: Kaplan-Meier of time to ICU admission or death in the asthma cohort, stratified by age (A) Under 55 years, (B) 55 years or more.

344x458mm (87 x 87 DPI)
Figure S11: Sensitivity analysis, stratifying asthma cohort by age, above or below 55 years of age, modelling for the outcome of COVID-19 hospitalisation. Analysed using stratified Cox models for the matched patients (matched on age, gender, and GP practice).

423x317mm (38 x 38 DPI)
Figure S12: Sensitivity analysis, only including asthma cohort age below 55 years of age, modelling for the outcome of COVID-19, pneumonia, or influenza hospitalisation. Analysed using stratified Cox models for the matched patients (matched on age, gender and GP practice) and adjusted for ethnicity, socioeconomic deprivation, obesity, diabetes, and cardiac disease.
Figure S13: Negative control outcomes in the asthma cohort, modelling for the outcomes of hospitalisation for diabetes, arm fracture or myocardial infarction. Analysed using stratified Cox models for the matched patients (matched on age, gender, and GP practice) and adjusted for ethnicity, socioeconomic deprivation, obesity, diabetes, cardiac disease, CVA, CRF and dementia.

402x292mm (38 x 38 DPI)
Figure S14: Association between allergic rhinitis and each COVID-19 outcome in the allergic rhinitis cohort. Analysed using stratified Cox models for the matched patients (matched on age, gender, and GP practice) and adjusted for ethnicity, socioeconomic deprivation, obesity, diabetes, cardiac disease, cerebrovascular disease, chronic renal failure and dementia.

415x307mm (38 x 38 DPI)