What is the association between inhaled corticosteroid use and risk of A&E attendance or death from COVID-19?

Study Protocol

Version: v2.0

Date: 2 June 2020

This is a collaboration between the following institutions as part of openSAFELY.org:

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- Electronic Health Records Research Group, Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine

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Amendments

Date	Original Version	Resulting Version	Section	Summary of Change	Rationale
2 June 2020	v1.0	v2.0	Template	Add Table of Content	Make Navigation Easier
2 June 2020	v1.0	v2.0	Template	Add Amendment Section	Allow for Protocol Amendments
2 June 2020	v1.0	v2.0	Inclusion/ Exclusion Criteria	COPD population: - Change other respiratory conditions exclusion time frame to ever - Exclude patients currently receiving a LTRA	Other respiratory conditions are chronic, and therefore these patients should be excluded to allow for a more homogeneous population. LTRA are an asthma drug, and patients with both COPD and asthma should be excluded.
2 June 2020	v1.0	v2.0	Inclusion/ Exclusion Criteria	Asthma population: - Change other respiratory conditions exclusion time frame to ever - Exclude patients currently receiving a LAMA if not also receiving an ICS	Other respiratory conditions are chronic, and therefore these patients should be excluded to allow for a more homogeneous population. LAMA alone tends to be given for COPD, and patients with both COPD and asthma should be excluded.
2 June 2020	v1.0	v2.0	Figure of Inclusion/ Exclusion Criteria	Change the covariate and exposure definitions from before or on index date, to before index date.	Outcomes can occur on and after the 1st of March, all other variables should be defined before this point.
2 June 2020	v1.0	v2.0	Covariates	- Reclassify diabetes into controlled and uncontrolled based on Hb1AC measures, remove insulin. - Remove oral steroid use as a covariate	Hb1AC is well recorded and a better indication of diabetic severity than insulin use. Oral steroid use is a blunt indication of copd/asthma severity, and this is likely better captured with the exacerbation variable.
2 June 2020	v1.0	v2.0	Outcomes	Change the primary outcome from death recorded in CPNS to death recorded in ONS	At the time of writing v1.0 of the protocol, CPNS had more

					up-to-date death information than ONS. However, during the programming of the initial analyses this changed, and ONS could provide more up-to-date death information than CPNS. As a greater number of deaths were captured in ONS compared to CPNS, and ONS captures population level outcomes rather than restricted to those in hospital, it was decided this was a more appropriate end-point.
2 June 2020	v1.0	v2.0	Exploratory Objectives	Change of negative control outcome from ILI to non-COVID deaths	ILI had been speculated to potentially be an appropriate control end-point, however, upon reflection non-COVID deaths were considered a more suitable negative control as it was anticipated this would be associated with underlying disease severity but not independently with the treatment exposures of interest.

Introduction

The outbreak of a novel coronavirus, SARS-Cov-2, in Wuhan, China in early December 2019 has developed into a global pandemic of unprecedented scale and consequence. As of the 8th of May 2020, almost 4 million people had been infected worldwide; approximately 270,000 people died of the disease the virus causes – COVID-19[1]. In England cases have also grown dramatically since the start of the outbreak, with more than 200,000 people having laboratory confirmed infections, of whom more than 30,000 have died[2]. Early descriptive data suggest that patients with more severe COVID-19 outcomes – hospitalisation or death – tend to be older and have pre-existing comorbidities[3–6]. In particular, descriptions of patients in China suggested hypertension, cardiovascular disease and diabetes were more common among patients with severe disease[3], although these did not take into account differences in age or gender among patients with or without severe disease.

As SARS-Cov-2 is a respiratory virus, it might be expected that patients with pre-existing respiratory conditions – such as chronic obstructive pulmonary disease (COPD) and asthma – would be particularly susceptible to infection, and once infected, that they would also tend to experience worse outcomes. However, rather surprisingly, early reports of COVID-19 patient characteristics described a very low prevalence of pre-existing respiratory conditions[3,7]. A descriptive study of 140 hospitalised COVID-19 patients in Wuhan found a COPD prevalence of 1.4%, whereas Guan et al's description of 1,099 outpatient and inpatient COVID-19 patients in the same area found a COPD prevalence of 1.1%[3,8]. Early analyses of the first few hundred cases in the UK also found an unexpected protective effect of asthma (McDonald 2020, personal communication), and whilst our research collaboration found an association between asthma and hospital death from COVID-19 using the OpenSAFELY platform, the effect size was surprisingly modest[6] . Although other data from the UK and US have since reported prevalences of respiratory conditions that are closer to expectations[5,9], the early data from Wuhan led to speculations that some treatments used in chronic respiratory diseases, specifically inhaled corticosteroids (ICS), may have a protective effect against SARS-Cov-2 infection or the development of symptoms that lead to diagnosis[7,10]

Inhaled corticosteroids (ICS) are glucocorticoids that are used to reduce inflammation, oedema, and mucus secretions in the airways and lungs. They have four main effects; anti-inflammatory, immunosuppressive, anti-proliferative/anti-mitotic and vasoconstrictive[11]. Although they cause less systemic effects than oral steroids they are associated with a higher risk of pneumonia in COPD[12–14]. Systemic steroid adverse effects, such as adrenal suppression may occur, if high doses are prescribed for a long time. Recent evidence from an in-vitro study has indicated that a specific ICS (Ciclesonide) can suppress the replication of SARS-CoV-2[15], and one other ICS in combination therapy with other medication, (budesonide in combination with glycopyrronium and formoterol) has been shown to inhibit the production of cytokines after cells were exposed to HCoV-229E, another human coronavirus[16]. A recent rapid review of the role of ICS in SARS-COV-2, SARS-COV-1, and MERS did not find any studies investigating the impact of prior ICS use on outcomes in either infection[10]. It is currently uncertain whether ICS influence the risk of developing COVID-19, either by increasing or decreasing it, and, once infected, whether ICS can affect the clinical prognosis of COVID-19 disease[10].

Epidemiological data investigating this hypothesis is scarce, although there are two ongoing randomised controlled trials investigating the role of ICS in patients hospitalised with laboratory confirmed COVID-19 and mild COVID-19 respectively[17,18]. Results from these trials are not expected to become available for some time with estimated study completion dates of July and Sept 2020 respectively, and, regardless of their findings, they will not answer questions related to the impact of long-term regular use of ICS. Further insights into the role of ICS use in COVID-19 may be gained from well-designed analyses of routinely collected electronic health record data. We therefore set out to explore the impact of recent ICS use on outcomes in COVID-19 disease using linked data from over 17 million patients in England.

Objectives

The specific objectives of the study are:

Primary Objectives

1. Estimate the effect of ICS use on the risk of death due to COVID-19 adjusting for confounding variables, among people with COPD living in England.
2. Estimate the effect of ICS use on the risk of death due to COVID-19 adjusting for confounding variables, among people with asthma living in England.

Secondary Objectives

1. Estimate the effect of ICS use and risk of the following outcomes due to COVID-19 among people with COPD living in England.
    a. A&E attendance due to suspected/definite COVID-19
2. Estimate the effect of ICS use and risk of the following outcomes due to COVID-19 among people with asthma living in England:
    a. A&E attendance due to suspected/definite COVID-19

Initially, results for the primary objective only will be presented. Further development work is ongoing to understand the data required to define the secondary outcome reliant on A&E attendance

Exploratory Objectives

1. If either a positive or negative effect of ICS use is found, use quantitative bias analysis to quantify the strength of unmeasured confounding that would need to be present for the association to have been solely explained by unmeasured confounding.
2. Evaluate how any association between ICS use and death due to COVID-19 varies by estimated ICS adherence.
3. If either a positive or a negative effect of ICS use is found, we will re-run the analyses using a negative control outcome - non-COVID deaths.

Methods

Data Source

We will use data from general practice (GP) records, obtained from the GP software provider The Phoenix Partnership (TPP), linked to COVID-19 inpatient ONS death certifications. The data will be accessed, linked and analysed through OpenSAFELY.org - a new data analytics platform created to address urgent questions relating to the epidemiology and treatment of COVID-19 in England, hosted by TPP. OpenSAFELY provides a secure software interface that allows NHS records to be pseudonymised, linked and analysed in near real-time; the GP patient data held on OpenSAFELY never leaves TPP's secure environment; other datasets are linked to it.

The research dataset analysed through OpenSAFELY is based on GP records retrieved from the TPP SystmOne electronic health record system. These data include diagnoses, medicines, physiological parameters, such as body mass index and vital signs, prior investigations, such as blood test results, and basic sociodemographics for almost 24 million individuals – approximately 40% of the English population. Data extracted by TPP SystmOne have previously been used in medical research, as part of the ResearchOne dataset. These records were subsequently linked to data from a number of other organisations who were directed under the Health Service (Control of Patient Information) Regulations 2002 to make their data available for COVID-19 research with the openSAFELY initiative. Currently, linkage is possible to: (1) the NHSE/NHSX Emergency Care Data Set (ECDS), which contains data on emergency attendance at A&E clinics across England; (2) the NHSE/NHSX Second Generation Surveillance System (SGSS) data on SARS-COV-2 test results; (3) the Intensive Care National Audit & Research Centre (ICNARC) Case Mix Programme, containing data on COVID-19 related Intensive Treatment Units (ITU) admissions; (4) the NHSE/NHSX COVID-19 Patient Notification System (CPNS) data on deaths among COVID-19 inpatients occurring in hospitals; and (5) Office for National Statistics (ONS) death data, which includes information on all deaths, including those due to non-COVID-19 causes as well as those occurring outside the hospital setting.

All data is held in a secure research environment hosted by TPP, which is a Tier 3 data centre, accredited to NHS Digital standards for centrally hosted clinical systems (ISO 27001 standard and IG Toolkit version 2).

Study Design and Population

We will use a population based cohort design to address our research questions. Patients will be followed from the 1st of March 2020, considered the start of risk for experiencing the outcomes due to the dynamics of the coronavirus outbreak in the UK, until the last date of data availability. Patients who do not experience the outcome of interest will be censored at the last date of data availability, death due to other causes recorded in ONS, or the date patients are transferred away from TPP, whichever comes first. The last date of data availability was considered seven days before the last death occurring in ONS, due to a reporting lag of approximately seven days.

From the raw data, we will select two cohorts with asthma or COPD, as follows:

Cohort 1: Asthma

Individuals meeting the following criteria will be included:

Inclusion criteria:

1. A record of asthma in the TPP primary care record within 3 years prior to 1st of March 2020. This approach has been used to identify patients with asthma in recent work based on clinical respiratory and electronic health record (EHR) research experience within the study team[19,20]. Recently coded illness was considered to be a reliable way of identifying currently active disease and avoids including people with earlier misdiagnosed disease.
2. ≥18 years of age and ≤110 years of age at the 1st of March 2020
3. Recorded male or female gender in TPP primary care record at the 1st of March 2020

Exclusion criteria

1. Less than 12 months of primary care records whilst registered in a TPP practice available at the 1st of March 2020, which may preclude adequate characterisation of potentially important confounding variables and recording of asthma.
2. A diagnosis of COPD or other chronic respiratory conditions within ever prior to 1st of March 2020.
3. Receiving nebulised asthma medication in the last 12 months. This tends to represent more severe disease; these patients were excluded to help assemble a more homogeneous population.
4. Receiving an LTRA, which might indicate that the patient has asthma.
5. A very small number of patients (<1%) are anticipated to have a missing Index of multiple deprivation (IMD) status and will be excluded from the analysis.

Cohort 2: COPD

Individuals meeting the following criteria will be included

Inclusion criteria:

1. A diagnosis of COPD in the TPP primary care record any time prior to 1st of March 2020.
2. ≥35 years of age and ≤110 years of age at the 1st of March 2020 (representing older profile of COPD patients)
3. Recorded male or female gender in TPP primary care record at the 1st of March 2020
4. Record of ever smoking (either current or past) prior to 1st of March 2020

The additional inclusion criterion requiring people with COPD to have a record of smoking was taken as we anticipated there to be a number of inaccurate COPD diagnostic codes; a

diagnostic code in combination with a smoking record was considered the most reliable way to identify people with COPD.

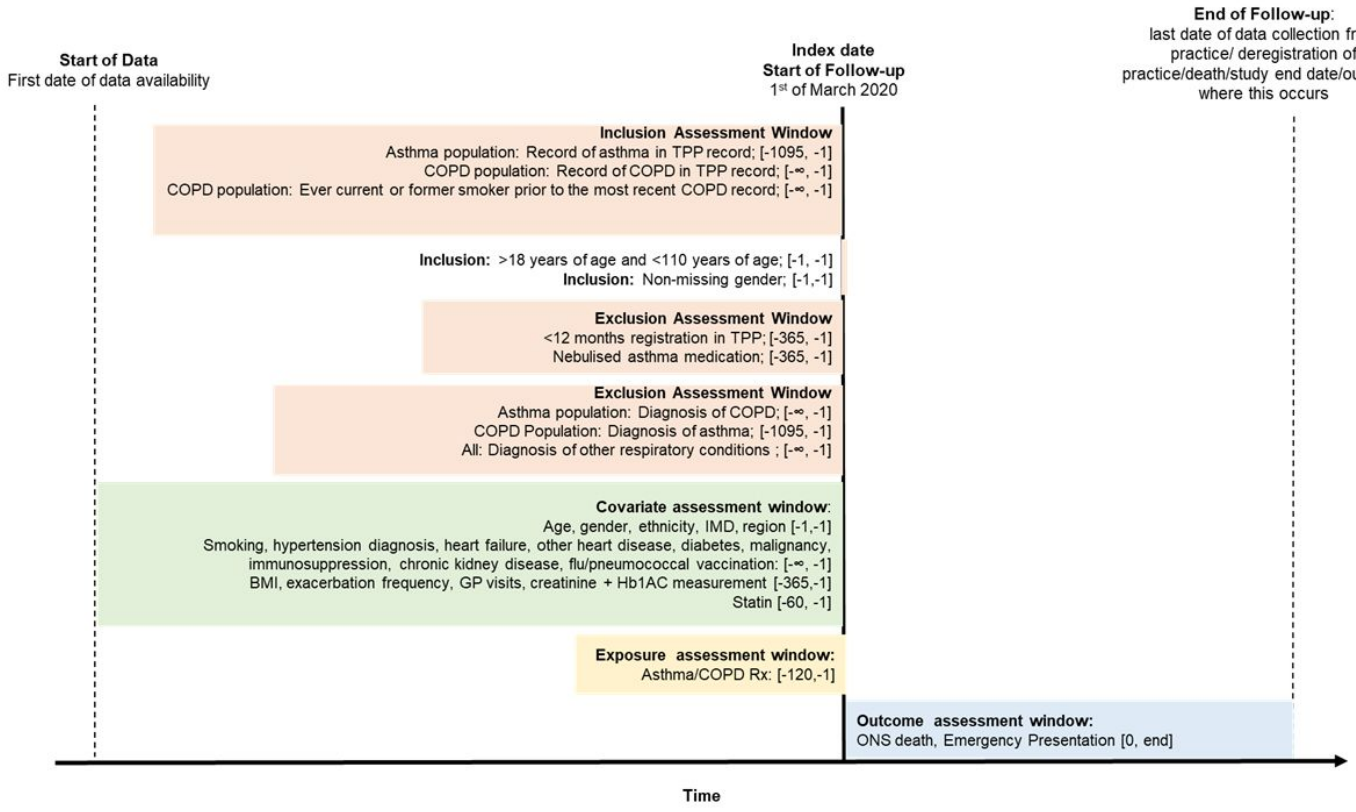
Exclusion criteria

1. Less than 12 months of primary care records available whilst registered in a TPP practice at the 1st of March 2020, which would preclude adequate characterisation of potentially important confounding variables.
2. Diagnosis of other chronic respiratory conditions ever prior to 1st Mar 2020
3. Diagnosis of asthma in the 3 years prior to 1st Mar 2020
4. Receiving nebulised COPD medication in last 12 months. This tends to represent more severe disease and is excluded to help assemble a more homogeneous population.
5. Receiving a LAMA (alone or in combination), as this is a medication which indicates the patient might have COPD.
6. A very small number of patients (<1%) are anticipated to have missing Index of multiple deprivation (IMD) status and will be excluded from the analysis

Note: for both asthma and COPD populations, expected exclusions due to recorded diagnosis of both asthma and COPD is ~14%, and the exclusion due to more than one other chronic respiratory condition is expected to be low.

The inclusion and exclusion criteria are illustrated in Figure 1.

Figure 1: Illustration of the Study Design



Study Measures

Discussions and decisions on every measure have been documented before implementing the final underlying code to complete the analysis. Detailed information on compilation and sources for every individual codelist is available at https://codelists.opensafely.org/ and the lists are available for inspection and re-use by the broader research community.

Exposure

The exposure of interest is the category of asthma/COPD medication prescribed in the 4 months prior to 1st Mar 2020 to capture usage in normal conditions. This date was chosen due to reports of substantial early and over-ordering of medicines and appeals by the NHS not to extend prescription durations in March. Therefore prescribing patterns from March may not represent usual usage e.g. with respect to levels of adherence. To investigate the impact of ICS use we need to compare against non-ICS treatment in both asthma and COPD. Specific exposure categories of interest are defined as follows:

COPD Exposures

There is some degree of treatment choice between ICS and non-ICS based therapies based on current NICE guidelines[21] and with this in mind, the primary definition for treatment categories is shown in Table 1. Patients receiving either no treatment, or no LAMA, LABA or ICS therapy will be described but will be excluded from the comparative analyses:

Table 1. Operational Definition for the COPD Drug Exposure of Interest

Variable	Variable level	Category	Definition	Timeframe
Drug Exposure	0	Non-ICS based therapy (LABA/LAMA)	Meeting both criteria: 1 At least one prescription in the LABA-LAMA combination list: https://codelists.opensafely.org/codelist/opensafely/laba-lama-combination-inhaler/ OR (at least one prescription of LABA https://codelists.opensafely.org/codelist/opensafely/single-ingredient-laba-inhalers/ AND at least one prescription of LAMA https://codelists.opensafely.org/codelist/opensafely/single-ingredient-lama-inhalers/) 2. No prescription for an ICS in the 4 months to 29 Feb 2020	4 months prior to 1st Mar 2020.
	1	ICS based combination therapy	Any COPD therapy that includes an ICS, in single or combination product in the 4 months to 29 Feb 2020 and meeting one of the following criteria: 1.Any prescription for a LABA+LAMA+ICS combination product https://codelists.opensafely.org/codelist/opensafely/laba-lama-ics-combination-inhaler/	

			2. Any prescription for a LABA+ICS combination product https://codelists.opensafely.org/codelist/opensafely/laba-ics-combination-inhaler/ 3. Any prescription for a single constituent ICS product AND (a prescription for a single constituent LABA or a prescription for a combination LAMA + LABA) https://codelists.opensafely.org/codelist/opensafely/high-dose-ics-inhalers/ https://codelists.opensafely.org/codelist/opensafely/low-and-medium-dose-ics-inhalers/ https://codelists.opensafely.org/codelist/opensafely/single-ingredient-laba-inhalers/ https://codelists.opensafely.org/codelist/opensafely/laba-lama-combination-inhaler/	

In COPD, people commonly receive two or more treatments, and the exposure of interest is any combination of therapy containing ICS. A further secondary exposure definition for COPD treatment is as follows, separating out patients on dual and triple therapy containing an ICS

- Non-ICS based treatment (baseline)
- ICS based dual therapy (LABA + ICS)
- ICS based triple therapy (LABA + LAMA + ICS)

Asthma Exposures

The primary exposure definition will be largely based on the ICS treatment pathway in current British Thoracic Society (BTS) treatment guidelines for adult asthma[22]. The strength of individual ICS products will be categorised according to current BTS guidance

All respiratory medications prescribed in the 4 months leading up to 1st Mar 2020 will be ascertained and used to categorise treatments as summarised in Table 2. Any other

non-ICS asthma therapy is permitted in all categories except the baseline which is defined as SABA only. We acknowledge that patients in the baseline group may differ in important ways from those prescribed ICS but are anticipating some degree of comparability based on respiratory disease clinical treatment experience within the study team. Furthermore, the stratification of ICS dose will help explore possible dose related patterns. Patients receiving no treatment for asthma will be described regarding baseline characteristics but will not be included in the comparative analyses .

Links are provided to the OpenSAFELY.org hosted codelists (OpenCodelists) for these variables. In the first planned analysis, we have analysed based on the product strength that has been prescribed. Likely dose taken is not simple to derive from the data, as dose syntax e.g. *Inhale one puff twice daily* is not readily available. Low and medium are grouped together due to overlap with higher strength products being easier to distinguish using this method.

Table 2. Operational Definition for the Asthma Drug Exposure of Interest

Variable	Variable level	Category	Definition	Timeframe
Drug Exposure	0	SABA only	Receiving a SABA, AND not receiving a LABA, ICS, or LTRA, singly or in combination in the 4 months to 29 Feb 2020. Prescription for any drug in the following category: Links to OpenCodelists definition	4 months prior to 1st Mar 2020.
	1	Low/medium dose ICS based therapy	Receiving a low/medium dose ICS with or without SABA, LABA, LTRA, singly or in combination in the 4 months to 29 Feb 2020: Links to OpenCodelists definition	
	2	High dose ICS based therapy	Receiving a high dose ICS with or without SABA, LABA, LTRA, singly or in combination in the 4 months to 29 Feb 2020: Links to OpenCodelists Definition of high dose ICS	

If patients have prescriptions for both low and medium/high ICS dose therapy, they will be categorised as receiving the most recent one. In a sensitivity analysis, these patients will be classified as receiving high-dose ICS.

Follow up and Outcomes

Follow up for each cohort will begin on 1st Mar 2020 and end at the latest of the outcome of interest in each analysis, and the date of last data availability. The primary outcome is death occurring due to suspected or confirmed COVID-19 in the ONS dataset. The secondary outcomes is presenting at an emergency unit with suspected or confirmed COVID-19 (ECDS data)

An operational definition for the primary outcome is provided in Table 3.

Table 3. Operational Definition for the Primary Outcome Variable

Variable	Definition	Timeframe
COVID-19 Death	Death information from ONS will be used to capture deaths occurring in and out of hospitals with laboratory confirmed or suspected COVID-19. ICD-10 codes will be used to identify COVID-19 related death outcomes in ONS. Specifically, the presence of the codes U071 or U072 as either the underlying cause or any of the up to 15 other causes of death.U	On or after the 1st of March 2020 until a week prior to the end of data availability, to account for an approximately week-long lag in data availability.

The diagnostic codes that will be used to identify the secondary, COVID-19 specific, outcomes are shown below, and all code (including early versions) for identifying these outcomes will be made public in the study github repository.

ICD-10 codes will be used to identify COVID-19 related outcomes in ONS:

- U071 COVID-19, virus identified
- U072 COVID-19, virus not identified

SNOMED codes to identify confirmed, suspected and probably COVID-19 disease in ECDS are yet to be determined.

Covariates

The covariates of interest were chosen following discussion with practising clinicians to identify potential important determinants of our exposure of interest (choice of asthma/COPD drug) and the outcomes of interest. The covariates which were pre-specified as potentially important confounding variables are listed below. Definitions and code lists are available at

https://codelists.opensafely.org/ and are available for inspection and re-use by the broader research community.

Unless otherwise specified, variables were created using diagnostic codes present ever in a patients' medical record.

- Age as of the 1st of March 2020
- Sex
- Ethnicity
- BMI, ascertained from weight measurements within the last 10 years, restricted to those taken when the patient was over 16 years old
- Smoking, most recent code prior to 1st of March 2020 (asthma only, as included by definition in COPD)
- Hypertension, using diagnostic codes only
- Heart Failure
- Other Heart Disease
- Diabetes, categorised as controlled (Hba1c < 58 mmols/mol), uncontrolled (Hba1c >= 58 mmols/mol) or Hb1AC not measured.
- Cancer
- Immunosuppression, including organ transplant, sickle cell anaemia and splenectomy
- Chronic Kidney Disease, using creatinine measurements within the year prior to the 1st of March 2020 OR ever having a code for renal dialysis
- GP consultation rate in the year prior to index dichotomized as 0 or >=1
- Flu vaccination status, between 1st Sep 2019 and 1st Mar 2020
- Pneumococcal vaccination status, 5 years prior to 01 Mar 2020
- Current Statin use, within 4 months of 1st of March 2020
- Index of Multiple Deprivation
- Geographic region
- COPD only:
    - Exacerbation history in the year prior to index - identified using a validated algorithm (Rothnie et al, 2015).
    - Prior history of asthma
- Asthma only: Exacerbation history in the year prior to index - identified using the process adopted by Bloom et al for moderate exacerbations identified using primary care records only [19].

Missing Data

In the primary analysis, those with missing BMI will be assumed non-obese and those with missing smoking information will be assumed to be non-smokers on the assumption that both obesity and smoking would be more likely to be recorded if present. We anticipate ~25% missing data on ethnicity and will exclude this variable from the primary models. A sensitivity analysis will be done amongst people with recorded ethnicity, adjusting for this variable in addition to the others. We anticipate ~5% missing data on GP consultation rate and will add this variable into a sensitivity analysis amongst those with complete recording of this variable. Patients with missing data on eGFR measurements, who do not have a code for end-stage renal disease, will be assumed to not have chronic kidney disease.

Statistical Analysis

Primary Objectives

As a first step, flowcharts showing the number of patients meeting each inclusion and exclusion criteria for the cohorts will be generated. The characteristics of patients in each cohort will be summarised using descriptive statistics, stratified by exposure status[25].

Time to the primary outcome, death due to COVID-19 as registered by ONS certification, will be displayed in Kaplan-Meier (KM) plots with time in study as the timescale. Cox regression will be used to estimate hazard ratios and 95% confidence intervals for the association between the categories in the drug class exposure variable and the outcome. Univariable models, models adjusted for age and sex as well as fully adjusted models, including all of the confounders listed in the covariates list, will be presented. Graphical methods and tests based on Schoenfeld residuals will be used to explore violations of the proportional hazards assumption. Post-hoc models including other adjustments, or removing some adjustment variables may be fit however, these will be clearly marked as post-hoc exploratory work in the presentation of any results. *A priori* we will determine whether the association between ICS exposure and death varies by age. There are no other pre-specified interactions between the treatment exposure of interest and the clinical variables, however, if an effect is found we will explore whether this varies according to calendar time (pre and post lockdown in the UK, 23rd of March). This investigation would depend on having a sufficient number of cases in our study population pre-lockdown.

Secondary Objectives

The methodology for the secondary outcomes will be as described for the primary objectives above.

Exploratory Objectives

If we detect a non-null association, we will investigate this further through the use of a negative control outcome, as we hypothesise that any effect of ICS on COVID-19 outcomes may be specific to COVID-19 and may not be expected to be seen with other outcomes. Originally, we had hypothesised that influenza like illness (ILI) during previous years might be a suitable negative control. However, death data was not available for prior calendar years, and we would have been restricted to identifying ILI diagnoses in primary care data. The outcome ascertainment would therefore have been markedly different for the negative control outcome, and we did not consider this to be a meaningful comparison with our primary outcome. In addition, there were concerns that ICS may have a potential, but not definitive, causal effect on ILI which would further complicate comparisons using this as a negative or indeed, positive, control.

ICS use was not anticipated to have a marked effect on the risk of dying from non-COVID causes. However, general frailty and disease severity, likely would increase the risk of dying from non-COVID causes. If any harmful association observed is due to confounding - that is, people who receive ICS are sicker than those who do not - we would expect to be able to observe a similarly increased risk of non-COVID death. Analyses will therefore be repeated using non-COVID death over the same time-period as a negative control outcome.

Secondly, for any non-null association, with 95% confidence intervals wholly above or below 1 in the primary analysis, we will conduct a quantitative bias analysis. This will estimate how strong unmeasured confounding would need to be in order to explain the association. We will use Ding and Vanderweele's e-value formulae, alongside probabilistic bias analysis, to estimate how strongly associated one or more unmeasured confounders would need to be with exposure and outcome to fully explain the observed association.

A final exploratory objective relates to defining exposure variables based on more detailed dosing instructions as well as estimated adherence. In the first planned analysis, we have grouped low and medium dose ICS together as a readily available dosing instruction decode facilitating assignment of low or medium ICS dose is not currently available. In future work, if/when this becomes available we aim to further separate low and medium dose. Similarly, in later work a secondary definition of exposure categories, based around likely treatment adherence will be defined if possible. The rationale for this is that any signal regarding a causal protective effect should be stronger in a more adherent group, assuming adherence doesn't change during the pandemic. Preliminary exposure groups, based on adherence, are listed below for the two populations:

<u>Asthma Cohort</u>

- SABA only (baseline)
- Any steroid with high adherence (>=70% by proportion of days covered in the previous 12 months)
- Any steroid with low adherence (<70% by proportion of days covered in the previous 12 months)
- Other

<u>COPD Cohort</u>

- Non-ICS based treatment (baseline)
- ICS based high adherence (>=70% in previous 12 months)
- ICS based low adherence (<70% in previous 12 months)

Sensitivity Analyses Objectives

We will also conduct a number of sensitivity analyses to evaluate the robustness of our results. This is anticipated to include:

1. For COPD analyses: redefine exposure categories separating dual and triple ICS therapy
2. For asthma analyses: Classify patients exposed to both low/medium and high ICS doses as receiving high dose ICS
3. For asthma analyses: Redefine the asthma population as anyone with an asthma record in the prior 3 years OR a record of asthma at any prior time, and receiving a prescription for an asthma medication in the last 4 months.

It should be noted that more sensitivity analyses may be added based on the initial results of analyses. These will be clearly marked as post-hoc analyses in any reporting of the results.

Table Shells

Note: Table shells are presented for the asthma population, and the primary objectives only. The tables will be adapted and repeated for the COPD population and for secondary objectives as required. Figures are not included as shells.

Figure 1: Flowchart of Patients

Table 1: Descriptive Characteristics

		Total	SABA	ICS		Other
				Medium/Low	*High*	
Total						
Age	18-<40					
	40-<50					
	50-<60					
	60-<70					
	70-<80					
	80+					
Gender	Female					
	Male					
BMI	<18.5					
	18.5-24.9					
	25-29.9					
	30-34.9					
	35-39.9					
	Missing					
Ethnicity	White					
	Mixed					
	Asian or Asian British					
	Black					

	Other					
	Missing					
IMD	1 (least deprived)					
	2					
	3					
	4					
	5 (most deprived)					
Smoking	Never					
	Current					
	Former					
	Missing					
Comorbidities	Hypertension					
	Heart Failure					
	Other Heart Disease					
	Diabetes					
	Cancer					
	Immunosuppression					
	CKD					
GP consultations	Median, IQR					
	Min, Max					
Vaccination	Flu					
	Pneumococcal					
Medications	Insulin					
	Statin					
	Oral Steroids					

Figure 2: Kaplan-Meier Plot of Time to in-hospital COVID-19 death, stratified by Treatment

[Note: Including number under follow-up at each time-point, for each treatment category]

Table 2: Hazard Ratios (HRs) and 95% confidence intervals (CI) for in-hospital COVID-19 death

		N (%) with the outcome	Unadjusted	Age-Sex Adjusted	Fully Adjusted
			HR (95% CI)	HR (95% CI)	HR (95% CI)
Treatment	SABA only (reference)		1.00	1.00	1.00
	ICS (low/medium dose)				
	ICS (high dose)				
	Other				

Figure 3: Forest Plots of Hazard Ratios (HRs) and 95% confidence intervals (CI) for in-hospital COVID-19 death

Strengths and Limitations

The strengths of this study will include the size of the source population: openSAFELY represents one of the largest EHR databases in Europe. This will allow analyses to have as high power as is possible during this stage of the pandemic. The primary outcome, death as recorded by ONS, is also being recorded and analysed in near real-time, which will allow the number of outcome events to be maximised and, again, ensuring analyses are as well powered as possible. The richness of the EHR will allow us to characterise patients' medical history with a relatively high degree of accuracy, as we will not be relying on data being collected during the pandemic to characterise comorbidities. This should allow us to better control for confounding by indication compared to studies conducted solely in the hospital setting. Other strengths will include the pre-specified objectives and analysis plan, which will clearly allow readers to see which hypotheses and analyses were planned in advance. Finally, all source code that is used both to define the study population and run the analysis will be made publicly available for other researchers to both re-use and scrutinize.

However, there are also limitations which should be borne in mind when interpreting any results. Notably these limitations would tend to apply to any study addressing this question using observational data, and are not unique to this study. Firstly, although we will attempt to reduce confounding by indication by choosing a restricted study population, using active comparators where available as well as adjusting for potentially important confounders, we cannot rule out that confounding by indication will remain after this – either due to variables we have not measured, or those we have measured imperfectly. Confounding by indication is a particular concern in the asthma population, where we anticipate most patients will be treated with an ICS, though we will be able to take advantage of the use of SABA only in patients who ought to be prescribed an ICS. Nonetheless, based on early analyses from the openSAFELY.org risk factor analyses, we would expect patients with more severe asthma to have worse outcomes than those with less severe asthma[6]. If our analyses are subject to confounding by indication due to asthma severity, we might therefore expect to observe an increasing risk of death among patients prescribed ICS compared to those prescribed SABA. The direction of this bias may therefore cause us to miss a true protective effect of ICS, should one exist. However, given how little we know about COVID-19 disease, and the unclear nature of individual patient behaviour changes during the pandemic, it is also possible that biases could operate in different directions. Treatment group comparability may be closer for the COPD cohort where we rely on some degree of patient/prescriber choice driving the decision over ICS based and non-ICS based therapy. However, we are aware that if NICE guidance on COPD treatment is very closely adhered to, the exposure groups may differ in important ways and our comparative analysis relies on a degree of non-guidance based prescribing. Comparisons of baseline characteristics will help us explore this, as will the secondary exposure definition where dual and triple ICS-based regimens are separated. The expectation here is that those receiving triple therapy are likely to have more severe COPD than those receiving dual therapy. To aid the interpretation of our results, for all detected associations we will quantify the strength an unmeasured confounder or group of unmeasured/imperfectly measured confounders would need to have to remove the observed association using so-called e-values.

Any changes over time in the relationship between the exposures of interest and the outcomes will be evaluated as part of checking the assumption of proportional hazards in the

Cox regression models. Deviations from proportional hazards will be considered and explored carefully, as we would not expect a true pharmacological association to vary over time, even as the pandemic progresses. Nonetheless, there may be reasons we cannot detect a true association during the different stages of the pandemic. For example, if asthmatics are shielding as the pandemic progresses, there may be fewer events among these patients as time goes on. Although the relative effect of the exposure should remain the same, the resulting lack of power could impact the precision by which this can be estimated.

Our analyses are also subject to risk of exposure misclassification. We have a broad exposure definition to capture patients who may have stockpiled medication prior to lockdown, however, we do not know whether or not patients with these prescriptions were truly taking the medications as prescribed. In addition, we did not have readily available information on doses for asthma medications, which meant that we had to categorise low and medium dose ICS together.

Given the inherent limitations of the study design, our results should be taken as hypothesis generating. Multiple studies of different designs, in different populations, will be needed before a conclusive answer relating to the impact of ICS exposure on COVID-19 infection risk and outcomes can be given.

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