

Inhaled corticosteroid use and risk COVID-19 related death among 966,461 patients with COPD or asthma: an OpenSAFELY analysis

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Abstract

Background: Early descriptions of the coronavirus outbreak showed a lower prevalence of asthma and COPD than was expected for people diagnosed with COVID-19, leading to speculation that inhaled corticosteroids (ICS) may protect against infection with SARS-CoV-2, and development of serious sequelae. We evaluated the association between ICS and COVID-19 related death using linked electronic health records in the UK.

Methods: We conducted cohort studies on two groups of people (COPD and asthma) using the OpenSAFELY platform to analyse data from primary care practices linked to national death registrations. People receiving an ICS were compared to those receiving alternative respiratory medications. Our primary outcome was COVID-19 related death.

Findings: We identified 148,588 people with COPD and 817,973 people with asthma receiving relevant respiratory medications in the four months prior to 01 March 2020. People with COPD receiving ICS were at a greater risk of COVID-19 related death compared to those receiving a long-acting beta agonist (LABA) and a long-acting muscarinic antagonist (LAMA) (adjusted HR = 1.38, 95% CI = 1.08 – 1.75). People with asthma receiving high dose ICS were at an increased risk of death compared to those receiving a short-acting beta agonist (SABA) only (adjusted HR = 1.52, 95%CI = 1.08 – 2.14); the adjusted HR for those receiving low-medium dose ICS was 1.10 (95% CI = 0.82 – 1.49). Quantitative bias analyses indicated that an unmeasured confounder of only moderate strength of association with exposure and outcome could explain the observed associations in both populations.

Interpretation: These results do not support a major role of ICS in protecting against COVID-19 related deaths. Observed increased risks of COVID-19 related death among people with COPD and asthma receiving ICS can be plausibly explained by unmeasured confounding due to disease severity.

Funding: This work was supported by the Medical Research Council MR/V015737/1.

Keywords: COVID-19, Pulmonary Disease, Chronic Obstructive; Asthma; Steroids; Pharmacoepidemiology

Introduction

The ongoing pandemic due to the novel coronavirus, SARS-CoV-2, has now affected over 7 million people worldwide with at least 400,000 people having died with COVID-19¹. People with more severe COVID-19 outcomes, including hospitalisation or death, tend to be older and have pre-existing comorbidities^{2,3,4,5,6,7,8}. Severe outcomes are often a result of lung complications, such as acute respiratory distress syndrome (ARDS) and respiratory failure. However, early reports of COVID-19 patients described an unexpectedly low prevalence of chronic respiratory conditions among hospitalised patients⁹. Although other studies suggest that chronic lung diseases, including chronic obstructive pulmonary disease (COPD), increase the risk of severe outcomes⁶⁻⁸, reported effect sizes for asthma have been modest^{6,7}. This has led to speculation that treatments for respiratory disease, specifically inhaled corticosteroids (ICS), may have a protective effect against SARS-CoV-2.⁹⁻¹¹

ICS are used to reduce airway inflammation, oedema, and mucus secretions. In-vitro evidence indicates that the ICS ciclesonide can suppress SARS-CoV-2 replication¹², and budesonide combined with glycopyrronium and formoterol inhibits the production of cytokines in cells exposed to HCoV-229E, another human coronavirus¹³. The oral/IV steroid dexamethasone has recently been shown to reduce the risk of death in severe COVID-19¹⁴. Conversely, although ICS have low systemic absorption, they have been associated with increased risk of developing pneumonia in people with COPD¹⁵⁻¹⁷, as well as other systemic steroid-related adverse effects¹⁸. A recent systematic review of the role of ICS in SARS-CoV-2, SARS-CoV-1, and MERS found no studies investigating the impact of prior ICS use on outcomes in any of these infections¹⁰.

We therefore set out to explore the association between current ICS use and outcomes in COVID-19, using the OpenSAFELY platform which contains linked primary care electronic health record data for approximately 40% of the population in England.

Methods

Study Design

We conducted two cohort studies using primary care electronic health record (EHR) data linked to death data from the Office for National Statistics (ONS). The index date (start of follow up) for both cohorts was 01 Mar 2020; follow-up lasted until 06 May 2020.

Data Source

Primary care records managed by the GP software provider The Phoenix Partnership (TPP) were linked to ONS death data through OpenSAFELY, a data analytics platform created by our team on behalf of NHS England¹⁹ to address urgent COVID-19 research questions ⁷ (<https://opensafely.org>). OpenSAFELY provides a secure software interface allowing the analysis of pseudonymised primary care patient records from England in near real-time within the EHR vendor's highly secure data centre, avoiding the need for large volumes of potentially disclosive pseudonymised patient data to be transferred off-site. This, in addition to other technical and organisational controls, minimises the risk of re-identification. Similarly pseudonymised datasets from other data providers are securely provided to the EHR vendor and linked to the primary care data. The dataset analysed within OpenSAFELY is based on 24 million people currently registered with GP surgeries using TPP SystemOne software. It includes pseudonymised data such as coded diagnoses, medications and physiological parameters. No free text data is included.

Study Populations

The COPD cohort included adults older than 35 years with COPD and current or former smoking recorded any time before the index date²⁰. We excluded people with prior diagnoses of other chronic respiratory conditions, or with asthma in the three years before the index date²¹, and those receiving nebulised COPD medications in the twelve months before the index date or a leukotriene receptor antagonist (indicating potential asthma) in the four months before the index date.

The asthma cohort included adults older than 18 years with asthma recorded within three years prior to the index date. People with COPD or other chronic respiratory conditions prior to the index date were excluded, as were those receiving a LAMA without an ICS, as this indicates possible COPD²².

People with missing data for gender, index of multiple deprivation (IMD), or less than one year of primary care records were excluded (supplemental figure 1).

Exposures

In the COPD population, people issued at least one ICS prescription within four months prior to the index date either in combination with LABA or LAMA/LABA, or as single therapy provided there was also at least one prescription record of a LABA, were compared with those with a prescription for a LABA/LAMA (combined or as separate single therapy prescriptions) only²². We did not include patients receiving LAMA monotherapy, as we were expecting greater clinical comparability between the LAMA/LABA and ICS-based therapy groups.

In the asthma population, people prescribed high dose ICS and low/medium-dose ICS during the four months before index date were compared with those prescribed SABA only. Exposure for people prescribed both high and low/medium dose ICS was assigned according to their most recent prescription. Inhalers were assigned to low/medium or high dose based the OpenPrescribing.net prescribing explorer which was developed based on BTS/SIGN guidance²³. Studies have shown that a significant percentage of people with asthma receiving SABA only are eligible for ICS treatment²⁴, suggesting they have similar disease severity to those receiving ICS and therefore represent a reasonable comparator group. The characteristics of all other people are described in supplementary material (supplemental table 1-2), however they are excluded from regression models to avoid comparisons to individuals not prescribed drugs of interest²⁵.

Outcomes

The outcome was COVID-19 related death as registered in ONS data using ICD-10 codes U07.1 (“COVID-19, virus identified”) and U07.2 (“COVID-19, virus not identified”) listed either as the underlying or any contributing cause of death. The latter ICD-10 code is used when laboratory testing is inconclusive or unavailable²⁶.

Covariates

Potential determinants of exposures and outcomes were identified by reviewing literature and through discussions with practising clinicians. As this is a study of current users, determinants of exposures include both factors that may affect the initial choice of treatment as well as those that influence whether patients remain on a certain treatment. The final list of potential confounders can be seen in box 1. Our methodology for creating codelists associated with these confounders has been previously described⁷: this included clinical and epidemiological review and sign-off by at least two authors. Detailed information on every codelist is shared at <https://codelists.opensafely.org/>.

Statistical Methods

Individuals characteristics were summarised using descriptive statistics, stratified by exposure status. Time to the primary outcome is displayed in Kaplan-Meier (KM) plots with time in study as the timescale. The competing risk of death from non-COVID-19 causes was dealt with by analysing the cause-specific hazard, with people dying from other causes censored at their date of death²⁷. We used cause-specific Cox regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between exposure categories and the outcome in each population. Univariable models, models adjusted for age (using restricted cubic splines) and sex as well as fully adjusted models including all covariates were fitted. Region was included as a stratification variable in fully adjusted models. We evaluated an *a priori* specified interaction between ICS exposure and age, to see if we could distinguish a differential effect in groups known to be at higher risk.

Sensitivity Analyses

In sensitivity analyses, first, we split the exposure categories in the COPD population to examine the effect of ICS with LABA/LAMA (triple combination) and ICS with LABA (dual combination) separately, anticipating greater underlying disease severity in people receiving triple therapy. Second, we restricted analyses to the largest ethnicity group (i.e., white British) to exclude any substantial confounding by ethnicity. We did not adjust for ethnicity in the main models as this was not anticipated to be a strong confounder and due to a sizable

proportion of individuals with missing ethnicity (~25%). In the asthma population, we varied the sample definition to include people with asthma diagnosed at any time, and a recent prescription for any asthma medication.

Negative Control Outcomes

We hypothesised that disease severity, but not ICS use, may influence the risk of non-COVID-19 related death. Analyses were therefore conducted using non-COVID-19 death as a negative control outcome censoring people at time of COVID-19 related death. If any potentially harmful association observed in primary analyses was due to confounding (i.e. people prescribed ICS had more severe underlying respiratory disease than those who did not) we expected to observe a similar association with non-COVID-19 related death in people prescribed ICS.

Quantitative Bias Analysis

We used e-value formulae to calculate the minimum strengths of association between an unmeasured confounder and exposure or outcome, conditional on measured covariates, necessary to fully explain observed associations²⁸.

Software and Reproducibility

Data management was performed using Python 3.8 and SQL, with analysis carried out using Stata 16.1. All of the code used for data management and analyses is openly shared online for review and re-use (<https://github.com/opensafely/ics-research>). All iterations of the pre-specified study protocol are archived with version control (<https://github.com/opensafely/ics-research/tree/master/protocol>).

Patient and Public Involvement

Patients were not formally involved in developing this specific study design that was developed rapidly in the context of a global health emergency. We have developed a publicly available website <https://opensafely.org/> through which we invite any patient or member of the public to contact us regarding this study or the broader OpenSAFELY project. The protocol and draft paper have been sent to the Asthma UK and British Lung Foundation Partnership for review from an expert-patient perspective.

Results

Patient Characteristics

148,488 people with COPD and 817,973 people with asthma and a relevant prescription within the four months before 01 Mar 2020 were included (supplemental figure 2-3).

COPD Population

Table 1 (see end) shows the characteristics of the COPD population. 43,278 (29%) received a LABA/LAMA prescription in the 4 months before index, and 105,210 (71%) prescriptions for ICS+LABA or ICS+LABA/LAMA. Demographic characteristics of treatment groups were similar; median age was 71 (IQR = 63 - 77) in the LABA/LAMA group and 72 (IQR = 64 - 78) in the ICS group, and just over half were men (54.5% in the LABA/LAMA group and 53.7% in the ICS group).

The presence of comorbidities was similar across the two treatment groups, except prior asthma diagnosis, which was more common among ICS recipients (12.9% in the LABA/LAMA group compared to 27.7% in the ICS group). The percentage of people with an exacerbation in the last year was lower in the LABA/LAMA group (19.7% vs 26.0%).

Asthma Population

Table 2 (see end) shows the characteristics of the asthma population. Most (608,583, 74%) had a prescription for low/medium dose ICS in the four months prior to index date; fewer received high dose ICS (101,010, 12%) and SABA only (108,380, 13%).

The asthma treatment groups differed in terms of demographic and clinical characteristics. The median age was 48 (IQR = 35 - 60), 53 (IQR = 40 - 66), and 55 (IQR = 44 - 67) for SABA only, low/medium dose ICS and high dose ICS respectively. The proportion of men was highest in the SABA group (43.0%), followed by the low/medium dose ICS (40.3%) and high dose ICS (38.2%).

The prevalence of most comorbidities was lowest among people in the SABA only group and highest in the high dose ICS group. The proportion with an asthma exacerbation in the past year increased markedly across treatment groups (14.0%, 20.0% and 36.3% among SABA, low/medium dose and high dose ICS respectively).

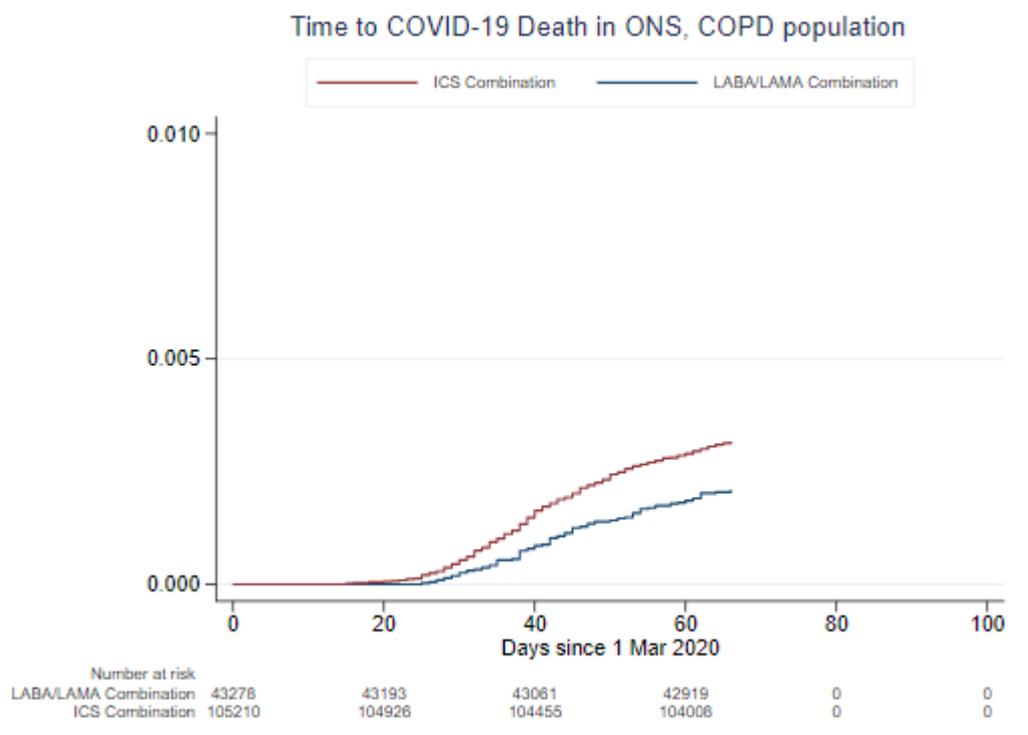
Univariable and Multivariable Results

COPD

421 COVID-19 related deaths occurred in the treated COPD population; time to COVID-19 related death by treatment group can be seen in Figure 1a. In univariable models, ICS use was associated with an increased risk of COVID-19 related death (HR = 1.52, 95% CI = 1.20 - 1.91; Figure 2). This association decreased on adjustment for age and gender, and the remaining comorbidities (aHR = 1.38; 95% CI = 1.08 - 1.75; Figure 2). Post-hoc analyses revealed that adjustment for prior exacerbations as a binary variable and smoking status (current/former) had the largest impact on reducing the hazard ratio (supplemental table 6). There was no evidence of a (pre-specified) interaction with age (supplemental table 4). We

detected significant deviations from the proportional hazards assumptions by testing for a zero slope in the scaled Schoenfeld residuals as well as by graphical inspection of plots of the Schoenfeld residuals against time (supplemental table 5, figure 4-6). The KM curve indicated that the hazard ratio was likely above one throughout the follow-up, with the effect size growing over time.

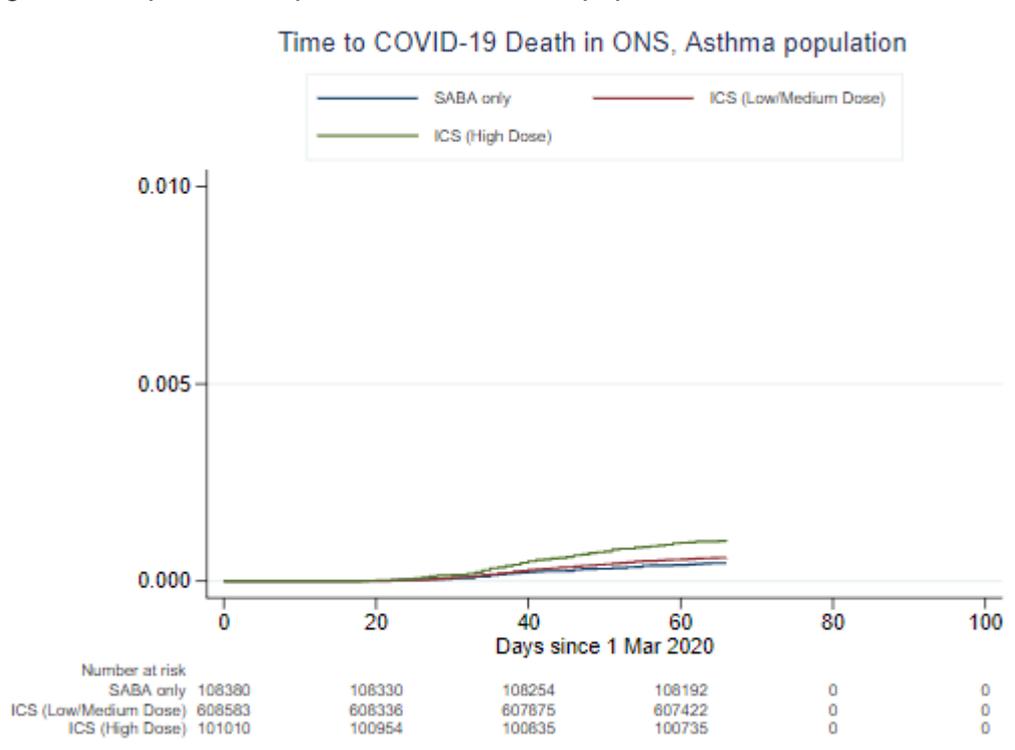
Figure 1a: Kaplan-Meier plots in the COPD population



Asthma

There were 515 COVID-19 related deaths in the treated asthma population; time to COVID-19 related death by treatment group can be seen in Figure 1b. In univariable models, receipt of both low/medium dose and high dose ICS was associated with an increased risk of COVID-19 related death (HR = 1.32, 95% CI = 0.98 - 1.77 and HR = 2.28, 1.62 - 3.20 respectively; Figure 3). These associations reduced markedly upon adjustment for age and gender, and the remaining pre-specified comorbidities (aHR = 1.10, 95% CI = 0.82 - 1.49 and aHR = 1.52, 95% CI = 1.08 - 2.14 for low/medium dose and high dose ICS respectively; Figure 3). Post-hoc analyses revealed that the greatest reduction in the strength of the association after the age and sex adjustment was adjustment for previous exacerbations (supplemental table 10). There was no evidence for a (pre-specified) interaction with age, and no deviations from the proportional hazards assumption (supplemental table 8 and 9, figure 7-12).

Figure1b: Kaplan-Meier plots in in the asthma population



Sensitivity Analyses

Figure 2 and 3 show results from sensitivity analyses. When considering receipt of ICS + LABA and ICS + LABA/LAMA separately in the COPD population, the risk of death was higher among those receiving ICS + LABA/LAMA (aHR = 1.41 95% CI = 1.10 - 1.81) but less markedly amongst those receiving ICS + LABA (aHR = 1.29, 95% CI = 0.95 - 1.74). Restricting analyses to people of white ethnicity to attempt to control for potential confounding by ethnicity led to a reduction in the hazard ratios in the COPD population (Figure 2), but not in the asthma population (Figure 3). Changing the population definition for the asthma population had a negligible impact on the results (Figure 3).

Figure 2: *Univariable and Multivariable Models, COPD population*

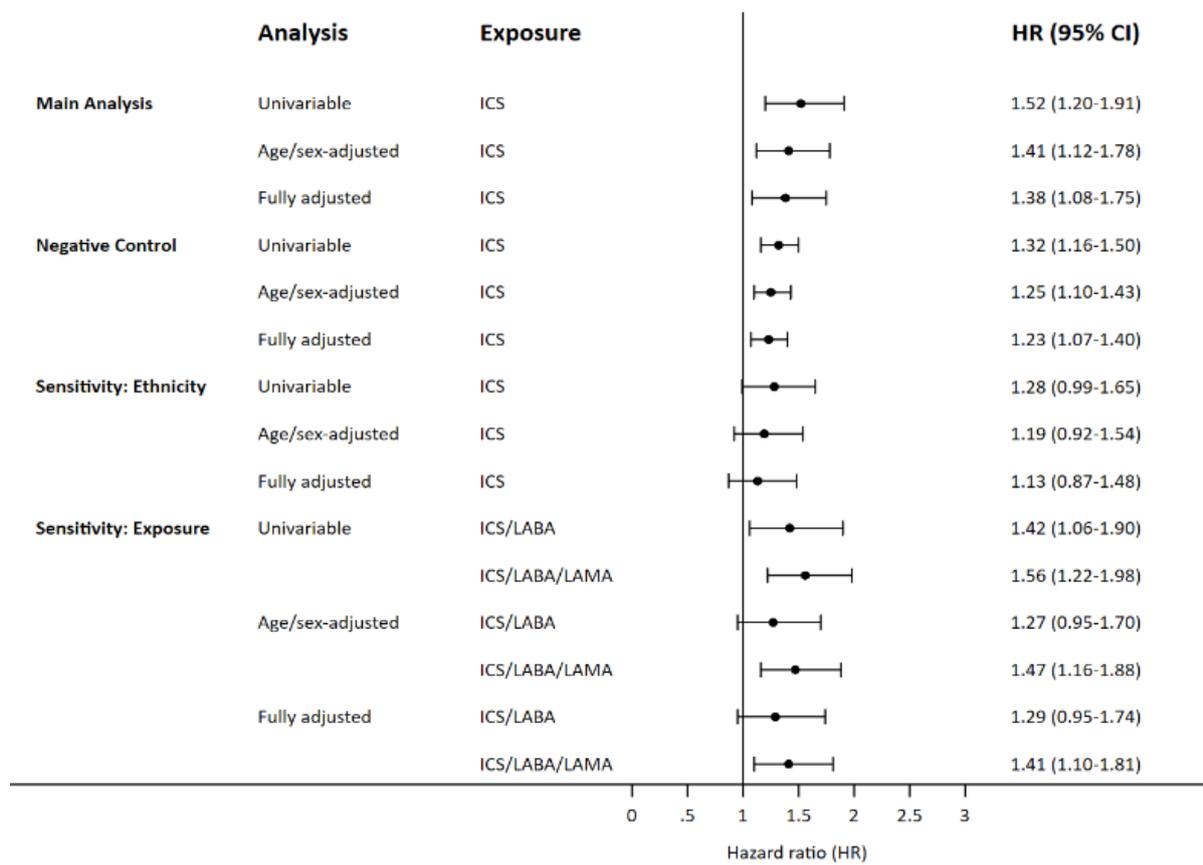
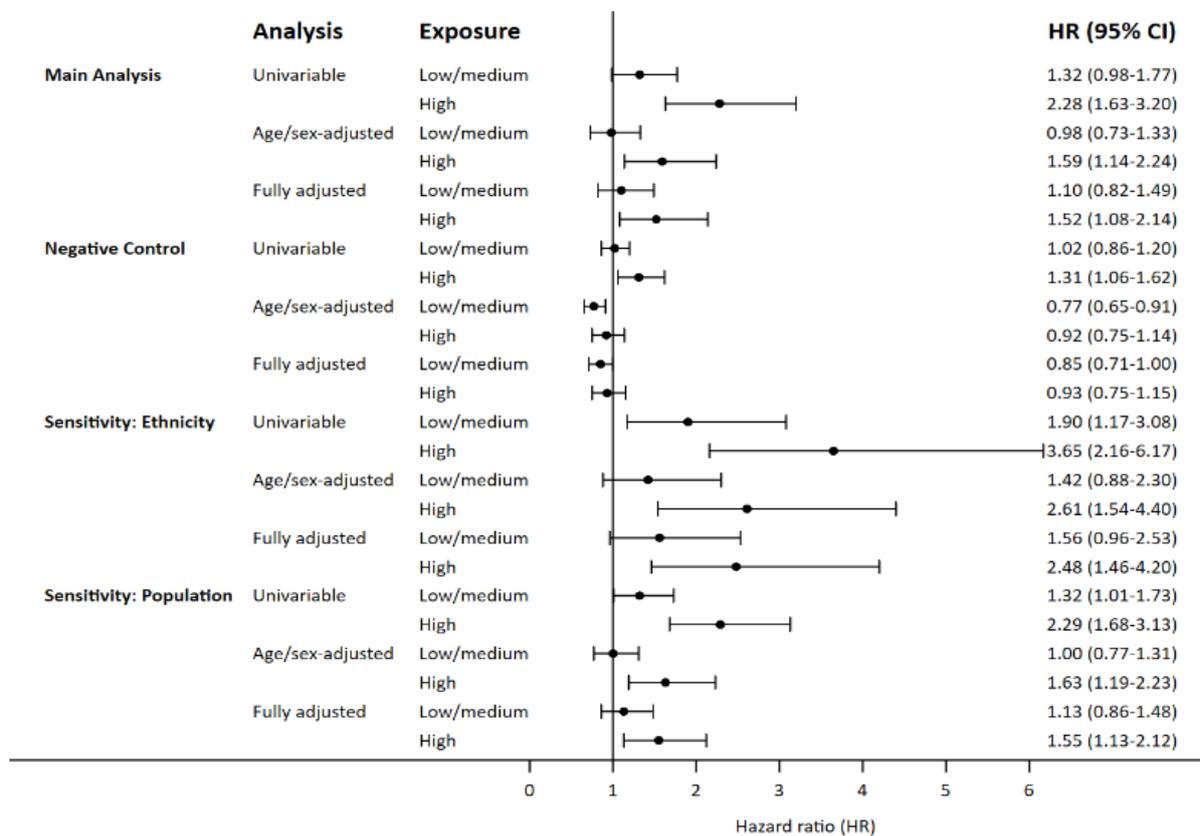


Figure 3: *Univariable and Multivariable Models, Asthma population*



Negative Control Analysis

In the COPD population, the risk of non-COVID-19 related death was higher among individuals in the ICS combination group with an adjusted HR = 1.23 (95% CI = 1.07 - 1.40). In the asthma population, there was no evidence of an association between receipt of high or low/medium dose ICS and non-COVID-19 related death with adjusted HRs of 0.85 (95% CI = 0.71 - 1.00) and 0.93 (95% CI = 0.75 - 1.15), respectively.

Quantitative Bias Analysis

To fully explain the lower bound of the 95% CI in the COPD cohort (1.08), or for the high-dose ICS association in the asthma cohort (1.08), an unmeasured confounder would need to be associated (conditional on measured covariates) with either exposure or outcome by at least risk ratio (RR) 1.37 (e-value/high threshold) and with both exposure and outcome by at least RR 1.08 (low threshold; Figure 4a-b). An unmeasured confounder would need to have a stronger association with either exposure or outcome to move the observed HRs to a clinically meaningful protective effect of 0.8 (high threshold COPD: 2.84, asthma: 3.21, supplemental figure 14-15; low threshold COPD: 1.73, asthma: 1.90).

Figure 4a: *E-value for the lower 95% CI and point estimate in the COPD*

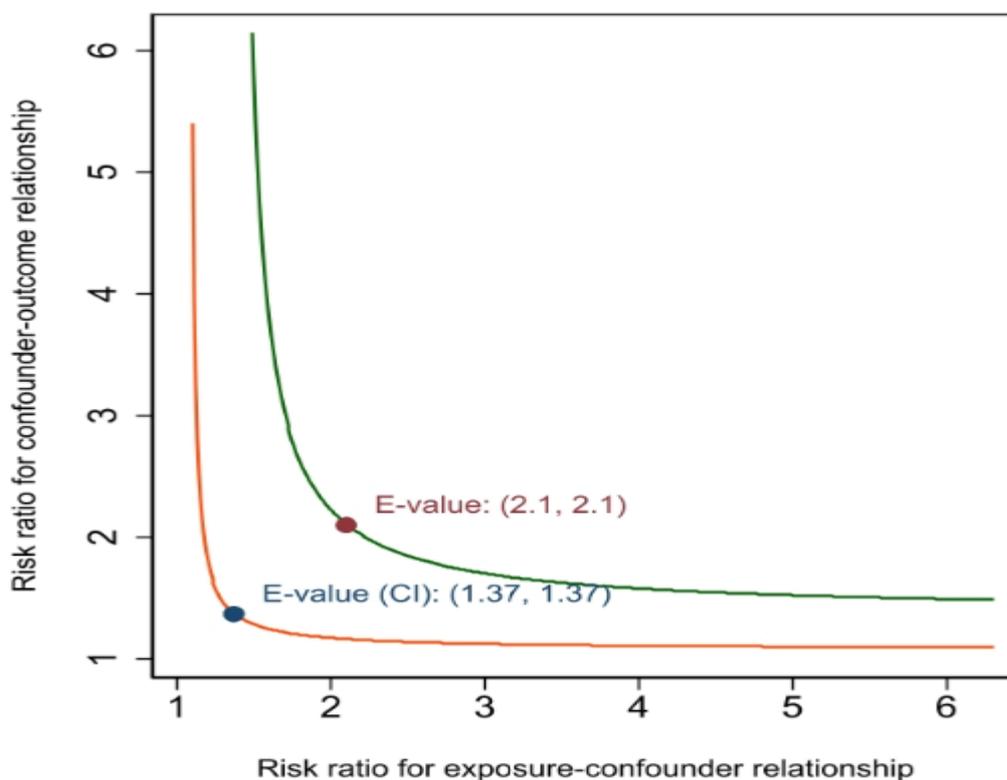
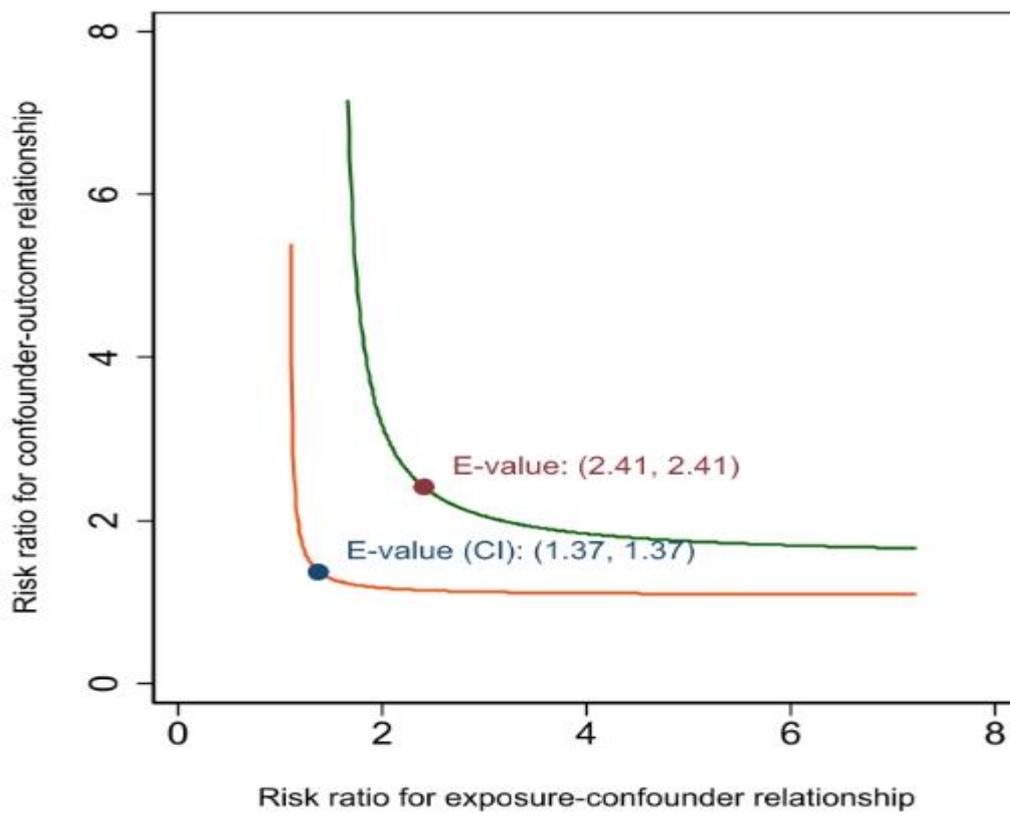


Figure 4b: *E*-value for the lower 95% CI and point estimate in the Asthma population



Discussion

Summary

This is the first study to investigate the association between regular ICS use and COVID-19 related death. Compared with non-ICS based treatments, ICS in people with COPD was associated with a ~40% increased risk of COVID-19 related death. In people with asthma, high dose ICS use was associated with an ~50% increased risk of COVID-19 related death, with little evidence of any association for low/medium dose ICS. Our findings do not provide any strong support for a protective effect from ICS use in these populations, as has been previously hypothesised. Our analyses overall indicate that the observed harmful associations could readily be explained by confounding due to underlying health differences between people prescribed ICS and those using other medications for asthma and COPD, rather than a causally harmful effect of ICS. Specifically, we observed a stronger association with COVID-19 related death between ICS triple therapy than ICS dual therapy in the COPD cohort; the ICS content of these two regimens is similar, and a causal effect of ICS would be expected to be comparable in these two groups. If we had successfully controlled for disease severity differences between treatment groups, we would also expect to see no association between ICS and the negative control outcome of non-COVID-19 death. The harmful association we observed suggests we had not perfectly captured all markers of disease severity, resulting in an association that is unlikely to be causal. The null finding between ICS and non-COVID-19 related death in the asthma cohort is less surprising, since asthma is less markedly associated with overall mortality compared to COPD²⁹. Finally, quantitative bias analysis confirms that a hypothetical unmeasured confounder of modest strength could fully explain the observed results.

Findings in Context

A literature review (box 2) found no other epidemiological studies or randomised controlled trials (RCTs) assessing the role of ICS in COVID-19. Two ongoing RCTs investigating the role of ICS in people hospitalised with laboratory confirmed COVID-19 and mild COVID-19 respectively (NCT04331054, NCT04330586) are due to complete later this year. The hypothesis of a protective effect of ICS in COVID-19 was based partly on the prevalence of chronic lung disease among outpatient and inpatient COVID-19 in China. However, more recent studies do not support initial assertions that people with chronic lung diseases (including COPD) are significantly underrepresented among COVID-19 patients^{6,7,30}. In addition, a number of studies have found that people with COPD are at greater risk of severe COVID-19 and death from COVID-19 once infected^{6,7}. The evidence for asthma in COVID-19 is more varied, with studies reporting both null and moderately harmful associations^{6,7}. It may be that features other than ICS use, such as shielding, influence the risk of acquiring SARS-CoV-2 among asthmatics. Studies investigating the causal effect of chronic respiratory disease, including COPD, and asthma on SARS-CoV-2 infection risk and COVID-19 disease, ideally taking into account the relatively large degree of heterogeneity that exists within each of these diagnostic categories, are urgently needed to help inform about levels of risk for these patients.

Strengths and weaknesses

The greatest strength of this study was the power we had to look at multiple drug treatments as our dataset included medical records from almost 24 million individuals. Our study is

further strengthened by the use of two different study populations and active comparators, as well as sensitivity analyses to quantify the potential impact of unmeasured confounding on results. Another strength is our use of open methods: we pre-specified our analysis plan and have shared all analytical code.

We also recognise possible limitations. The primary limitation is the risk of confounding by indication due to unmeasured or imperfectly defined potential confounding variables. Decisions regarding treatment choices involve factors that may not be well recorded in electronic health records including measures such as spirometry, and likely steroid responsiveness. As we did not have secondary care data our assessment of exacerbation history was incomplete, limiting our ability to adjust for this. Our sensitivity analyses confirm that unmeasured confounding is a plausible reason for the harmful associations we observed. The proportional hazards assumption was not met for the COPD models, with KM plots indicating that the hazard ratio for this exposure increased over time. This is perhaps not surprising, as the risk of acquiring COVID-19 was lower in the early stages of the pandemic. The HR for the COPD population should be interpreted as an average over the entire follow-up period. Finally, it is important to note that the outcome of COVID-19 related death will reflect the risk both of becoming infected as well as the risk of developing severe disease and dying. It is possible that ICS use has a different effect on the risk of infection and on disease severity.

Policy Implications and Future Research

We find no evidence that ICS has a strongly beneficial effect on COVID-19 related mortality, and therefore we cannot recommend that they are used to treat people with COVID-19 outside of the context of RCTs. Importantly, from the totality of the evidence provided here, including our sensitivity analyses, our results do not support the interpretation that regular ICS therapy for asthma or COPD increases risk of death from COVID-19, and do not provide evidence to support adjustments in ICS therapy among COVID-19 patients. Future observational studies of this clinical question are likely to face similar challenges around unmeasured confounding.

The UK has an unusually large volume of detailed longitudinal patient data. We have demonstrated that it is feasible to rapidly address specific hypotheses about medicines in a transparent manner inside the secure environment of an EHR vendor in order to minimise the large volumes of potentially disclosive data that would otherwise have to move into separate systems. We will use the OpenSAFELY platform to further inform the global response about drug treatments during the COVID-19 emergency.

Summary

We found no evidence of a beneficial effect of regular ICS use on COVID-19 related mortality. Although we report a small harmful association, the pattern of results we observed suggests this could readily be explained by differences in underlying health between people receiving ICS and those receiving other respiratory medications. People currently taking ICS should continue taking them if recommended as part of routine care.

Table 1. Demographic and Clinical Characteristics - COPD

		Total	LABA/LAMA Combination	ICS Combination	Other
Total Included		291,805 (100.0)	43,278 (100.0)	105,210 (100.0)	143,317 (100.0)
Demographics					
Grouped age	18 - <40	1,232 (0.4)	85 (0.2)	184 (0.2)	963 (0.7)
	40 - <50	10,028 (3.4)	1,060 (2.4)	2,289 (2.2)	6,679 (4.7)
	50 - < 60	40,910 (14.0)	5,746 (13.3)	12,237 (11.6)	22,927 (16.0)
	60 - <70	80,788 (27.7)	12,599 (29.1)	29,519 (28.1)	38,670 (27.0)
	70 - <80	104,319 (35.7)	16,092 (37.2)	40,370 (38.4)	47,857 (33.4)
	80+	54,528 (18.7)	7,696 (17.8)	20,611 (19.6)	26,221 (18.3)
	Age (years)	Median (IQR)	71 (63-77)	71 (63-77)	72 (64-78)
	Mean (SD)	69.76 (10.76)	70.03 (10.10)	70.76 (10.10)	68.95 (11.38)
	Min, Max	35, 103	35, 100	35, 102	35, 103
Male	No	133,738 (45.8)	19,699 (45.5)	48,707 (46.3)	65,332 (45.6)
	Yes	158,067 (54.2)	23,579 (54.5)	56,503 (53.7)	77,985 (54.4)
Grouped BMI	Underweight (<18.5)	11,359 (3.9)	1,682 (3.9)	4,744 (4.5)	4,933 (3.4)
	Normal (18.5-24.9)	89,195 (30.6)	12,938 (29.9)	31,858 (30.3)	44,399 (31.0)
	Overweight (25-29.9)	95,443 (32.7)	14,011 (32.4)	33,494 (31.8)	47,938 (33.4)
	Obese I (30-34.9)	55,541 (19.0)	8,590 (19.8)	20,278 (19.3)	26,673 (18.6)
	Obese II (35-39.9)	22,054 (7.6)	3,568 (8.2)	8,379 (8.0)	10,107 (7.1)
	Obese III (40+)	10,006 (3.4)	1,580 (3.7)	3,945 (3.7)	4,481 (3.1)
	Missing	8,207 (2.8)	909 (2.1)	2,512 (2.4)	4,786 (3.3)
Smoking status	Never	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Former	184,400 (63.2)	26,015 (60.1)	69,710 (66.3)	88,675 (61.9)
	Current	107,405 (36.8)	17,263 (39.9)	35,500 (33.7)	54,642 (38.1)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Ethnicity	White	218,717 (75.0)	32,455 (75.0)	79,682 (75.7)	106,580 (74.4)
	Mixed	676 (0.2)	92 (0.2)	186 (0.2)	398 (0.3)
	Asian or Asian British	3,366 (1.2)	258 (0.6)	835 (0.8)	2,273 (1.6)
	Black	1,208 (0.4)	103 (0.2)	302 (0.3)	803 (0.6)
	Other	1,060 (0.4)	113 (0.3)	286 (0.3)	661 (0.5)
	Unknown	66,778 (22.9)	10,257 (23.7)	23,919 (22.7)	32,602 (22.7)
Index of Multiple Deprivation (IMD)	Least Deprived	58,902 (20.2)	8,049 (18.6)	19,893 (18.9)	30,960 (21.6)
	2	58,779 (20.1)	8,419 (19.5)	20,619 (19.6)	29,741 (20.8)
	3	59,175 (20.3)	8,755 (20.2)	21,235 (20.2)	29,185 (20.4)
	4	57,633 (19.8)	8,431 (19.5)	21,634 (20.6)	27,568 (19.2)
	Most Deprived	57,316 (19.6)	9,624 (22.2)	21,829 (20.7)	25,863 (18.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatments					
Single SABA	No	125,025 (42.8)	12,349 (28.5)	21,544 (20.5)	91,132 (63.6)
	Yes	166,780 (57.2)	30,929 (71.5)	83,666 (79.5)	52,185 (36.4)
High Dose ICS	No	266,112 (91.2)	43,278 (100.0)	79,748 (75.8)	143,086 (99.8)
	Yes	25,693 (8.8)	0 (0.0)	25,462 (24.2)	231 (0.2)
Low/Medium Dose ICS	No	204,577 (70.1)	43,278 (100.0)	22,739 (21.6)	138,560 (96.7)
	Yes	87,228 (29.9)	0 (0.0)	82,471 (78.4)	4,757 (3.3)
Single ICS	No	284,499 (97.5)	43,278 (100.0)	102,887 (97.8)	138,334 (96.5)
	Yes	7,306 (2.5)	0 (0.0)	2,323 (2.2)	4,983 (3.5)
Single SAMA	No	288,487 (98.9)	43,120 (99.6)	103,725 (98.6)	141,642 (98.8)
	Yes	3,318 (1.1)	158 (0.4)	1,485 (1.4)	1,675 (1.2)

Single LABA	No	283,744 (97.2)	40,849 (94.4)	104,356 (99.2)	138,539 (96.7)
	Yes	8,061 (2.8)	2,429 (5.6)	854 (0.8)	4,778 (3.3)
Single LAMA	No	204,171 (70.0)	38,690 (89.4)	59,736 (56.8)	105,745 (73.8)
	Yes	87,634 (30.0)	4,588 (10.6)	45,474 (43.2)	37,572 (26.2)
LABA ICS	No	216,279 (74.1)	43,278 (100.0)	29,684 (28.2)	143,317 (100.0)
	Yes	75,526 (25.9)	0 (0.0)	75,526 (71.8)	0 (0.0)
LABA LAMA	No	245,652 (84.2)	1,929 (4.5)	100,406 (95.4)	143,317 (100.0)
	Yes	46,153 (15.8)	41,349 (95.5)	4,804 (4.6)	0 (0.0)
LABA LAMA ICS	No	258,774 (88.7)	43,278 (100.0)	72,179 (68.6)	143,317 (100.0)
	Yes	33,031 (11.3)	0 (0.0)	33,031 (31.4)	0 (0.0)
Single LTRA	No	291,805 (100.0)	43,278 (100.0)	105,210 (100.0)	143,317 (100.0)
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Clinical Conditions					
Chronic kidney disease	No	241,927 (82.9)	35,547 (82.1)	86,857 (82.6)	119,523 (83.4)
	Yes	49,878 (17.1)	7,731 (17.9)	18,353 (17.4)	23,794 (16.6)
Diagnosed hypertension	No	146,895 (50.3)	21,595 (49.9)	50,961 (48.4)	74,339 (51.9)
	Yes	144,910 (49.7)	21,683 (50.1)	54,249 (51.6)	68,978 (48.1)
Heart Failure	No	267,221 (91.6)	39,424 (91.1)	95,255 (90.5)	132,542 (92.5)
	Yes	24,584 (8.4)	3,854 (8.9)	9,955 (9.5)	10,775 (7.5)

Other Heart Diseases	No	226,356 (77.6)	33,233 (76.8)	81,114 (77.1)	112,009 (78.2)
	Yes	65,449 (22.4)	10,045 (23.2)	24,096 (22.9)	31,308 (21.8)
Cancer	No	251,789 (86.3)	37,060 (85.6)	90,144 (85.7)	124,585 (86.9)
	Yes	40,016 (13.7)	6,218 (14.4)	15,066 (14.3)	18,732 (13.1)
Diabetes Severity	No Diabetes	221,197 (75.8)	32,888 (76.0)	79,531 (75.6)	108,778 (75.9)
	Diabetes, not severe	51,265 (17.6)	7,583 (17.5)	19,011 (18.1)	24,671 (17.2)
	Diabetes, severe	18,561 (6.4)	2,711 (6.3)	6,363 (6.0)	9,487 (6.6)
	Diabetes, no Hb1AC	782 (0.3)	96 (0.2)	305 (0.3)	381 (0.3)
Recent Statin	No	150,420 (51.5)	20,517 (47.4)	50,894 (48.4)	79,009 (55.1)
	Yes	141,385 (48.5)	22,761 (52.6)	54,316 (51.6)	64,308 (44.9)
Flu vaccine	No	73,828 (25.3)	8,683 (20.1)	19,904 (18.9)	45,241 (31.6)
	Yes	217,977 (74.7)	34,595 (79.9)	85,306 (81.1)	98,076 (68.4)
Pneumococcal Vaccine	No	231,323 (79.3)	32,266 (74.6)	83,906 (79.8)	115,151 (80.3)
	Yes	60,482 (20.7)	11,012 (25.4)	21,304 (20.2)	28,166 (19.7)
Exacerbation in last year	No	236,123 (80.9)	34,748 (80.3)	77,858 (74.0)	123,517 (86.2)
	Yes	55,682 (19.1)	8,530 (19.7)	27,352 (26.0)	19,800 (13.8)
Asthma ever	No	236,592 (81.1)	37,705 (87.1)	76,033 (72.3)	122,854 (85.7)
	Yes	55,213 (18.9)	5,573 (12.9)	29,177 (27.7)	20,463 (14.3)
Immunosuppressed (combination algorithm)	No	290,160 (99.4)	43,073 (99.5)	104,672 (99.5)	142,415 (99.4)

	Yes	1,645 (0.6)	205 (0.5)	538 (0.5)	902 (0.6)
GP consultation count	Median (IQR)	9 (5-16)	10 (6-16)	10 (6-17)	8 (4-14)
	Mean (SD)	12.19 (11.62)	12.72 (11.32)	13.43 (12.26)	11.12 (11.12)
	Min, Max	0, 306	0, 276	0, 306	0, 268
Exacerbation Count	Median (IQR)	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-0)
	Mean (SD)	.26 (.63)	.26 (.60)	.38 (.77)	.17 (.48)
	Min, Max	0, 12	0, 9	0, 12	0, 8

Table 2. Demographic and Clinical Characteristics - Asthma

		Total	SABA only	ICS (Low/Medium Dose)	ICS (High Dose)	Other
Total Included		1,285,035	108,380 (100.0)	608,583 (100.0)	101,010 (100.0)	467,062 (100.0)
Demographics						
Grouped age	18 - <40	417,254 (32.5)	36,237 (33.4)	144,889 (23.8)	18,816 (18.6)	217,312 (46.5)
	40 - <50	235,356 (18.3)	22,051 (20.3)	107,786 (17.7)	18,454 (18.3)	87,065 (18.6)
	50 - < 60	253,115 (19.7)	21,846 (20.2)	130,346 (21.4)	23,742 (23.5)	77,181 (16.5)
	60 - <70	181,865 (14.2)	13,965 (12.9)	105,828 (17.4)	18,956 (18.8)	43,116 (9.2)
	70 - <80	130,554 (10.2)	9,206 (8.5)	79,729 (13.1)	13,888 (13.7)	27,731 (5.9)
	80+	66,891 (5.2)	5,075 (4.7)	40,005 (6.6)	7,154 (7.1)	14,657 (3.1)
	Age (years)	Median (IQR)	49 (35-62)	48 (35-60)	53 (40-66)	55 (44-67)
	Mean (SD)	49.32 (17.90)	48.32 (17.34)	53.13 (17.37)	55.01 (16.34)	43.36 (17.29)
	Min, Max	18, 106	18, 106	18, 106	18, 106	18, 105
Male	No	750,041 (58.4)	61,799 (57.0)	363,282 (59.7)	62,444 (61.8)	262,516 (56.2)
	Yes	534,994 (41.6)	46,581 (43.0)	245,301 (40.3)	38,566 (38.2)	204,546 (43.8)
Grouped BMI	Underweight (<18.5)	19,134 (1.5)	1,636 (1.5)	7,618 (1.3)	1,148 (1.1)	8,732 (1.9)
	Normal (18.5-24.9)	340,536 (26.5)	28,126 (26.0)	152,943 (25.1)	20,937 (20.7)	138,530 (29.7)
	Overweight (25- 29.9)	394,590 (30.7)	32,856 (30.3)	196,437 (32.3)	30,752 (30.4)	134,545 (28.8)
	Obese I (30-34.9)	239,220 (18.6)	20,060 (18.5)	122,118 (20.1)	22,281 (22.1)	74,761 (16.0)
	Obese II (35-39.9)	112,039 (8.7)	9,494 (8.8)	56,827 (9.3)	11,878 (11.8)	33,840 (7.2)
	Obese III (40+)	67,768 (5.3)	5,930 (5.5)	34,079 (5.6)	8,243 (8.2)	19,516 (4.2)
	Missing	111,748 (8.7)	10,278 (9.5)	38,561 (6.3)	5,771 (5.7)	57,138 (12.2)

Smoking status	Never	589,698 (45.9)	45,361 (41.9)	268,746 (44.2)	41,200 (40.8)	234,391 (50.2)
	Former	497,853 (38.7)	42,250 (39.0)	254,169 (41.8)	44,111 (43.7)	157,323 (33.7)
	Current	195,370 (15.2)	20,611 (19.0)	85,366 (14.0)	15,655 (15.5)	73,738 (15.8)
	Missing	2,114 (0.2)	158 (0.1)	302 (0.0)	44 (0.0)	1,610 (0.3)
Ethnicity	White	882,703 (68.7)	74,312 (68.6)	427,754 (70.3)	71,237 (70.5)	309,400 (66.2)
	Mixed	12,970 (1.0)	983 (0.9)	5,032 (0.8)	848 (0.8)	6,107 (1.3)
	Asian or Asian					
	British	72,097 (5.6)	5,693 (5.3)	32,353 (5.3)	5,866 (5.8)	28,185 (6.0)
	Black	20,495 (1.6)	1,546 (1.4)	8,141 (1.3)	1,453 (1.4)	9,355 (2.0)
	Other	12,174 (0.9)	895 (0.8)	4,856 (0.8)	876 (0.9)	5,547 (1.2)
	Unknown	284,596 (22.1)	24,951 (23.0)	130,447 (21.4)	20,730 (20.5)	108,468 (23.2)
Index of Multiple Deprivation (IMD)	Least Deprived	260,435 (20.3)	21,069 (19.4)	124,381 (20.4)	17,767 (17.6)	97,218 (20.8)
	2	261,441 (20.3)	21,697 (20.0)	124,199 (20.4)	18,946 (18.8)	96,599 (20.7)
	3	258,380 (20.1)	21,978 (20.3)	121,807 (20.0)	20,187 (20.0)	94,408 (20.2)
	4	258,263 (20.1)	22,389 (20.7)	120,992 (19.9)	21,468 (21.3)	93,414 (20.0)
	Most Deprived	246,516 (19.2)	21,247 (19.6)	117,204 (19.3)	22,642 (22.4)	85,423 (18.3)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatments						
Single SABA	No	679,186 (52.9)	0 (0.0)	191,771 (31.5)	22,831 (22.6)	464,584 (99.5)
	Yes	605,849 (47.1)	108,380 (100.0)	416,812 (68.5)	78,179 (77.4)	2,478 (0.5)
High Dose ICS	No	1181109 (91.9)	108,380 (100.0)	605,667 (99.5)	0 (0.0)	467,062 (100.0)
	Yes	103,926 (8.1)	0 (0.0)	2,916 (0.5)	101,010 (100.0)	0 (0.0)
Low/Medium Dose ICS	No	668,905 (52.1)	108,380 (100.0)	0 (0.0)	93,463 (92.5)	467,062 (100.0)
	Yes	616,130 (47.9)	0 (0.0)	608,583 (100.0)	7,547 (7.5)	0 (0.0)

Single ICS	No	994,280 (77.4)	108,380 (100.0)	327,894 (53.9)	90,944 (90.0)	467,062 (100.0)
	Yes	290,755 (22.6)	0 (0.0)	280,689 (46.1)	10,066 (10.0)	0 (0.0)
Single SAMA	No	1282214 (99.8)	108,264 (99.9)	606,954 (99.7)	100,113 (99.1)	466,883 (100.0)
	Yes	2,821 (0.2)	116 (0.1)	1,629 (0.3)	897 (0.9)	179 (0.0)
Single LABA	No	1276523 (99.3)	107,837 (99.5)	602,628 (99.0)	99,510 (98.5)	466,548 (99.9)
	Yes	8,512 (0.7)	543 (0.5)	5,955 (1.0)	1,500 (1.5)	514 (0.1)
Single LAMA	No	1268654 (98.7)	108,380 (100.0)	600,539 (98.7)	92,673 (91.7)	467,062 (100.0)
	Yes	16,381 (1.3)	0 (0.0)	8,044 (1.3)	8,337 (8.3)	0 (0.0)
LABA ICS	No	853,659 (66.4)	108,380 (100.0)	270,615 (44.5)	7,602 (7.5)	467,062 (100.0)
	Yes	431,376 (33.6)	0 (0.0)	337,968 (55.5)	93,408 (92.5)	0 (0.0)
LABA LAMA	No	1284675 (100.0)	108,380 (100.0)	608,344 (100.0)	100,889 (99.9)	467,062 (100.0)
	Yes	360 (0.0)	0 (0.0)	239 (0.0)	121 (0.1)	0 (0.0)
LABA LAMA ICS	No	1283765 (99.9)	108,380 (100.0)	607,399 (99.8)	100,924 (99.9)	467,062 (100.0)
	Yes	1,270 (0.1)	0 (0.0)	1,184 (0.2)	86 (0.1)	0 (0.0)
Single LTRA	No	1215202 (94.6)	108,380 (100.0)	568,123 (93.4)	77,972 (77.2)	460,727 (98.6)
	Yes	69,833 (5.4)	0 (0.0)	40,460 (6.6)	23,038 (22.8)	6,335 (1.4)
Clinical Conditions						
Chronic kidney disease	No	1223801 (95.2)	103,287 (95.3)	573,168 (94.2)	93,958 (93.0)	453,388 (97.1)
	Yes	61,234 (4.8)	5,093 (4.7)	35,415 (5.8)	7,052 (7.0)	13,674 (2.9)

Diagnosed hypertension	No	976,993 (76.0)	82,562 (76.2)	432,272 (71.0)	67,177 (66.5)	394,982 (84.6)
	Yes	308,042 (24.0)	25,818 (23.8)	176,311 (29.0)	33,833 (33.5)	72,080 (15.4)
Heart Failure	No	1262657 (98.3)	106,402 (98.2)	596,019 (97.9)	98,019 (97.0)	462,217 (99.0)
	Yes	22,378 (1.7)	1,978 (1.8)	12,564 (2.1)	2,991 (3.0)	4,845 (1.0)
Other Heart Diseases	No	1206042 (93.9)	101,496 (93.6)	564,730 (92.8)	91,872 (91.0)	447,944 (95.9)
	Yes	78,993 (6.1)	6,884 (6.4)	43,853 (7.2)	9,138 (9.0)	19,118 (4.1)
Cancer	No	1217695 (94.8)	102,684 (94.7)	571,051 (93.8)	94,267 (93.3)	449,693 (96.3)
	Yes	67,340 (5.2)	5,696 (5.3)	37,532 (6.2)	6,743 (6.7)	17,369 (3.7)
Diabetes Severity	No Diabetes	1126195 (87.6)	93,542 (86.3)	523,583 (86.0)	83,022 (82.2)	426,048 (91.2)
	Diabetes, not severe	105,767 (8.2)	8,935 (8.2)	57,791 (9.5)	12,233 (12.1)	26,808 (5.7)
	Diabetes, severe	48,858 (3.8)	5,545 (5.1)	25,270 (4.2)	5,434 (5.4)	12,609 (2.7)
	Diabetes, no Hb1AC	4,215 (0.3)	358 (0.3)	1,939 (0.3)	321 (0.3)	1,597 (0.3)
Recent Statin	No	1064041 (82.8)	90,284 (83.3)	475,645 (78.2)	74,797 (74.0)	423,315 (90.6)
	Yes	220,994 (17.2)	18,096 (16.7)	132,938 (21.8)	26,213 (26.0)	43,747 (9.4)
Flu vaccine	No	667,064 (51.9)	65,150 (60.1)	240,729 (39.6)	35,986 (35.6)	325,199 (69.6)
	Yes	617,971 (48.1)	43,230 (39.9)	367,854 (60.4)	65,024 (64.4)	141,863 (30.4)
Pneumococcal Vaccine	No	1195495 (93.0)	101,794 (93.9)	557,468 (91.6)	91,049 (90.1)	445,184 (95.3)
	Yes	89,540 (7.0)	6,586 (6.1)	51,115 (8.4)	9,961 (9.9)	21,878 (4.7)

Exacerbation in last year	No	1075873 (83.7)	93,180 (86.0)	486,952 (80.0)	64,309 (63.7)	431,432 (92.4)
	Yes	209,162 (16.3)	15,200 (14.0)	121,631 (20.0)	36,701 (36.3)	35,630 (7.6)
Immunosuppressed (combination algorithm)	No	1260449 (98.1)	106,111 (97.9)	598,384 (98.3)	99,382 (98.4)	456,572 (97.8)
	Yes	24,586 (1.9)	2,269 (2.1)	10,199 (1.7)	1,628 (1.6)	10,490 (2.2)
GP consultation count	Median (IQR)	6 (3-12)	6 (3-12)	7 (4-13)	9 (5-16)	5 (2-10)
	Mean (SD)	9.26 (10.78)	9.22 (10.55)	10.21 (11.10)	12.77 (13.37)	7.28 (9.32)
	Min, Max	0, 604	0, 286	0, 548	0, 604	0, 604
Exacerbation Count	Median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-0)
	Mean (SD)	.296 (1.03)	.24 (.95)	.35 (1.09)	.812 (1.71)	.13 (.68)
	Min, Max	0, 17	0, 16	0, 17	0, 17	0, 16

Box 1: Prespecified hypothetical confounders

- Age
- Sex
- Body Mass Index (BMI): Measurement of weight in the last decade
- Indices of multiple deprivation (IMD): Quintiles from IMD 2019
- Diagnosed hypertension
- Heart disease: categorised as heart failure and other heart disease
- Diabetes: categorised as controlled (HbA1c < 58 mmol/mol), uncontrolled (HbA1c ≥ 58 mmol/mol) or HbA1c not measured within the last 12 months
- Cancer
- Immunosuppressive conditions: organ transplant, sickle cell anaemia and splenectomy
- Chronic kidney disease: based on creatinine measurements within the last 12 months or ever having a code for renal dialysis
- Influenza vaccination status: recorded between 01 Sep 2019 and 01 Mar 2020
- Pneumococcal vaccination status: record in the five years prior to 01 Mar 2020
- Statin use: recorded within four months prior to 1st of March 2020,
- Exacerbation history: different methods used for asthma³¹ and COPD population³² with COPD models additionally adjusted for a history of asthma.

Box 2: Research in Context

Evidence before this study

At the start of the global coronavirus outbreak, Inhaled Corticosteroids (ICS) were hypothesised to offer some protection against either infection with SARS-CoV-2 or against severe outcomes from COVID-19, such as acute respiratory distress syndrome (ARDS) and respiratory failure⁹, despite these medications being known to increase the risk of pneumonia and other respiratory tract infections^{17,33}. The hypothesis was based at least in part on epidemiological data showing a low prevalence of chronic respiratory disease among Chinese COVID-19 patients², although there was also some support of a potential protective effect from in-vitro studies^{12,13}. Most recently, ICS exposure has been found to correlate with a lower expression of ACE2 and TMPRSS2, the entry receptors used by SARS-CoV-2, in sputum cells³⁴. A recent systematic review evaluating whether administration of ICS was associated with clinical outcomes in COVID-19, SARS or MERS identified no relevant studies¹⁰.

Added value of this study

Our study was specifically designed to assess the role of pre-morbid ICS use in COVID-19. We included two cohorts of participants: people with asthma, and people with COPD, both of whom have a possible indication for ICS. Neither analysis was strongly suggestive that regular ICS therapy for asthma or COPD has a clinically important causal effect on COVID-19 mortality in either direction.

Our study has several key strengths: Firstly, it includes almost a million participants making it the largest contemporary study of ICS use to date. Secondly, we used active comparators and multiple sensitivity analyses to reduce and quantify the impact of possible unmeasured confounding. Finally, our analyses were pre-specified and we used open methods throughout the study with code and codelists available for examination and reuse.

Implications of all the available evidence

Evidence from our study and other research suggests there is neither a demonstrable benefit nor clear harm from ICS use against COVID-19 related mortality and therefore at present there is no evidence people should alter their ICS therapies during the pandemic. We also cannot recommend that ICS be used specifically to treat people with COVID-19 outside of the context of clinical trials. Future observational research is likely to be subject to similar issues around unmeasured confounding, and evidence from RCTs will provide more definitive answers regarding the role of ICS in COVID-19 later this year.

Administrative

Acknowledgements

We are very grateful for all the support received from the TPP Technical Operations team throughout this work; for generous assistance from the information governance and database teams at NHS England / NHSX.

Conflicts of Interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare the following: BG has received research funding from Health Data Research UK (HDRUK), the Laura and John Arnold Foundation, the Wellcome Trust, the NIHR Oxford Biomedical Research Centre, the NHS National Institute for Health Research School of Primary Care Research, the Mohn-Westlake Foundation, the Good Thinking Foundation, the Health Foundation, and the World Health Organisation; he also receives personal income from speaking and writing for lay audiences on the misuse of science. IJD has received unrestricted research grants and holds shares in GlaxoSmithKline (GSK).

Funding

This work was supported by the Medical Research Council MR/V015737/1. TPP provided technical expertise and infrastructure within their data centre *pro bono* in the context of a national emergency. BG's work on better use of data in healthcare more broadly is currently funded in part by: NIHR Oxford Biomedical Research Centre, NIHR Applied Research Collaboration Oxford and Thames Valley, the Mohn-Westlake Foundation, NHS England, and the Health Foundation; all DataLab staff are supported by BG's grants on this work. LS reports grants from Wellcome, MRC, NIHR, UKRI, British Council, GSK, British Heart Foundation, and Diabetes UK outside this work. JPB is funded by a studentship from GSK. AS is employed by LSHTM on a fellowship sponsored by GSK. KB holds a Sir Henry Dale fellowship jointly funded by Wellcome and the Royal Society. HIM is funded by the National Institute for Health Research (NIHR) Health Protection Research Unit in Immunisation, a partnership between Public Health England and LSHTM. AYSW holds a fellowship from BHF. RM holds a Sir Henry Wellcome fellowship. EW holds grants from MRC. RG holds grants from NIHR and MRC. ID holds grants from NIHR and GSK. RM holds a Sir Henry Wellcome Fellowship funded by the Wellcome Trust. HF holds a UKRI fellowship. The views expressed are those of the authors and not necessarily those of the NIHR, NHS England, Public Health England or the Department of Health and Social Care.

Funders had no role in the study design, collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Ethical approval

This study was approved by the Health Research Authority (REC reference 20/LO/0651) and by the LSHTM Ethics Board (ref 21863). No further ethical or research governance approval was required by the University of Oxford but copies of the approval documents were reviewed and held on record.

Guarantor

BG

Contributorship

Contributions are as follows:

Conceptualization LS BG ID;

Data curation CB JP JC SH SB DE PI CM;

Formal Analysis AS AJW BM CM JB;

Funding acquisition BG LS;
Information governance AM BG CB JP;
Methodology ID AS LT CTR AW KB EW SJWE JQ LS JB CM AJW BM SB BG;
Disease category conceptualisation and codelists CM AJW AS CTR PI SB DE CB JC JP SH
HD HC KB SB AM BM LT ID HM RM HF JQ;
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