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ORIGINAL ARTICLE

Association between inhaled corticosteroid use and COVID-19 outcomes

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Abstract

Background: Recent evidence has established a beneficial effect of systemic corticosteroids for treatment of moderate-to-severe COVID-19.

Objective: To determine if inhaled corticosteroid use is associated with COVID-19 outcomes.

Methods: In a nationwide cohort of hospitalized SARS-CoV-2 test-positive individuals in Denmark, we estimated the 30-day hazard ratio of intensive care unit (ICU) admission or death among users of inhaled corticosteroids (ICS) compared with users of bronchodilators (β_2-agonist/muscarinic-antagonists), and non-users of ICS overall, with Cox regression adjusted for age, sex, and other confounders. We repeated these analyses among influenza test-positive patients during 2010–2018.

Results: Among 6267 hospitalized SARS-CoV-2 patients, 614 (9.8%) were admitted to ICU and 677 (10.8%) died within 30 days. ICS use was associated with a hazard ratio of 1.09 (95% CI [CI], 0.67 to 1.79) for ICU admission and 0.78 (95% CI, 0.56 to 1.11) for death compared with bronchodilator use. Compared with no ICS use overall, the hazard ratio of ICU admission or death was 1.17 (95% CI, 0.87–1.59) and 1.02 (95% CI, 0.78–1.32), respectively. Among 10 279 hospitalized influenza patients, of which 951 (9.2%) were admitted to ICU and 1275 (12.4%) died, the hazard ratios were 1.43 (95% CI, 0.89–2.30) and 1.11 (95% CI, 0.85–1.46) for ICU admission, and 0.80 (95% CI, 0.63–1.01) and 1.03 (95% CI, 0.87–1.22) for death compared with bronchodilator use and no ICS use overall, respectively.

Conclusion: Our results do not support an effect of inhaled corticosteroid use on COVID-19 outcomes, however we can only rule out moderate-to-large reduced or increased risks.

Study registration: The study was pre-registered at encepp.eu (EUPAS35897).

KEYWORDS
cohort study, COVID-19, inhaled corticosteroids, pharmacoepidemiology

Key Points

- In a population cohort study of Danish COVID-19 patients, use of inhaled corticosteroids was not significantly associated with risk of admission to ICU or death within 30 days compared with no use.

Abbreviations: BMI, BODY mass index; CI, confidence interval; ICS, inhaled corticosteroid; ICU, intensive care unit.

- Compared with hospitalized influenza patients in 2010–2018, hospitalized SARS-CoV-2 patients had a similar high overall mortality, despite being younger and healthier, but there was no indication of different effects of inhaled corticosteroid use on disease outcomes.
- The findings overall argue for continued use of inhaled corticosteroids according to current guidelines during the COVID-19 pandemic.
- Sensitivity analysis of inhaled corticosteroid subtypes suggests a reduced risk of severe COVID-19 outcomes among users of inhaled budesonide.
- The protective association between inhaled budesonide and SARS-CoV-2 outcomes is in line with results from the randomized STOIC trial. Taken together, these findings argue for larger randomized trials of inhaled budesonide in early SARS-CoV-2 infection.

1 | INTRODUCTION

Infection with the novel coronavirus SARS-CoV-2, the causative agent of the COVID-19 pandemic, has only limited treatment options.[1–7] Studies report that SARS-CoV-2 infection often leads to severe airway inflammation[8] and recent randomized controlled trials found a substantial beneficial effect of systemic treatment with the corticosteroid dexamethasone in hospitalized COVID-19 patients requiring nasal oxygen or mechanical ventilation.[3–7] On the other hand, a tendency towards an adverse effect of per oral dexamethasone for patients not requiring oxygen was found in the RECOVERY trial. Nevertheless, the role of inhaled corticosteroids in morbidity of COVID-19 is unclear, with one study finding ambiguous results.[9] Adding to the uncertainty, pre-clinical studies suggests inhaled corticosteroids downregulate the SARS-CoV-2 receptors ACE2/TMPRSS2[10] and inhibit SARS-CoV-2 replication,[11] while there is evidence of more severe disease in COPD patients.[12,13]

Using Danish nationwide population registers on prescription drug use, laboratory-confirmed infectious disease, and hospitalizations, we present a nationwide cohort study of inhaled corticosteroid use and COVID-19 outcomes. To aid in the interpretation of the effects of inhaled corticosteroid use on COVID-19 morbidity in a real-world setting, we conducted a comparison analysis of the effect of inhaled corticosteroid use on influenza morbidity during the 2010–2018 influenza seasons, as randomized controlled trials has not found an association between inhaled corticosteroid use and influenza morbidity.[14]

2 | METHODS

2.1 | Materials

The Danish Civil Registration System allows individual-level linkage of information from national health registers, in addition to providing demographic information on the entire Danish population.[15] Information on PCR tests for SARS-CoV-2 and influenza infection is available through MiBA, the Danish Microbiology Database, which includes all microbiological test results in Denmark, starting from 2010.[16–18] The Danish National Patient Register covers information on hospital admission, admission to intensive care units (ICU), use of mechanical ventilation, and diagnostic codes to identify underlying comorbidities.[19] The Danish National Prescription Registry, which contains individual-level information on all filled prescriptions in Denmark, provides information on pharmaceutical exposures of interest.[20] The Cause of Death Register includes information on all registered deaths in Denmark.[21]

2.2 | Study population

All hospitalized individuals aged 40 years or older in Denmark with a positive SARS-CoV-2 PCR test up to July 16, 2020, were included in our COVID-19 cohort from the date of testing or hospitalization, whichever came latest. The COVID-19 cohort was followed up for ICU admission or death within 30 days from cohort entry. Individuals who tested PCR-positive for influenza during 2010–2018 were included in an equivalent influenza cohort from the date of testing or hospitalization, whichever came latest, and followed up for ICU admission or death within 30 days from cohort entry. For sensitivity analyses, we also constructed nationwide cohorts of all individuals aged 40 years or older who tested positive for SARS-CoV-2 or influenza while out-of-hospital to investigate effect of ICS use in the general population. These cohorts were followed up for hospitalization or death within 30 days from the test date. In addition, we constructed cohorts of SARS-CoV-2 or influenza test-positive ICU patients who were followed up for death within 30 days from admission to ICU, to investigate effect of ICS use among patients with severe illness.

2.3 | Study variables

Exposure groups were categorized as (1) ICS use: individuals with inhaled corticosteroid (ICS) use, defined as one or more filled prescriptions of inhaled corticosteroids within the last 6 months, with or without simultaneous filled prescriptions for other inhaled pharmaceuticals (i.e., β_2-receptor agonist and/or muscarinic receptor antagonists), or use of combinatory inhalers (e.g., combined ICS and β_2-receptor agonist inhaler), (2) Patients with bronchodilator use: individuals with β_2-receptor agonist and/or muscarinic receptor antagonists use

defined as one or more filled prescriptions within the last 6 months, but not ICS use, and (3) All patients without ICS use: individuals without ICS use. Prescriptions 2 weeks prior to a positive test were omitted when allocating study participants to exposure groups. Information on other covariates of interest was defined by relevant pharmaceutical, demographic, and diagnostic codes (see Table S1).

2.4 | Outcomes

The study aimed to investigate the effect of ICS on disease severity, why admission to ICU and death where chosen as primary endpoints as both outcomes represent severe infection. Information on date of admission to ICU and mechanical ventilation, respectively, was acquired from the Danish National Patient Register. Information on date of death was acquired from the Cause of Death Register.

2.5 | Statistical analysis

Our main analysis was conducted among hospitalized individuals who tested positive for SARS-CoV-2 (in 2020) and influenza (in 2010–2018), respectively. We followed participants for 30 days from the date of study entry until either ICU admission, or death. We used Cox proportional hazards regression to estimate the hazard ratios of death and ICU admission comparing exposure groups. We estimated 30-day cumulative hazards according to exposure status taking competing risks of respectively ICU admission or death into account using the Nelson–Aalen estimator. In the Cox models, we took potential confounders into account through direct propensity score adjustment, in addition to age, sex, β2-receptor agonist use, and muscarinic receptor antagonist use. We considered the following covariates in the propensity score: atrial fibrillation, dementia, heart failure, hypertension, inflammatory bowel disease, malignancy, renal failure, Charlson Comorbidity index score, number of filled prescription within 90 days, and per oral corticosteroid use. Covariate status was ascertained 6 months before study entry (before exposure ascertainment). Propensity scores were estimated using logistic regression of probability of exposure on the above-mentioned covariates as main effects. We estimated separate propensity scores for each exposure group of interest. Covariate balance was assessed by graphical inspection of propensity score distribution among exposed and non-exposed cohort members and no indications of unbalanced propensity scores were found (distribution of propensity scores by exposure group can be seen in Figures S1–S4 for the COVID-19 cohort and Figures S5–S8 for the influenza cohort in the supplement). Lastly, a graphical overview of the study design is shown in Figure S9.

3 | RESULTS

Our COVID-19 cohort included 6267 individuals who had been hospitalized with a positive SARS-CoV-2 test up to and including December 15, 2020, while our influenza cohort included 10 279 individuals hospitalized with a positive influenza test during 2010–2018. Among the hospitalized SARS-CoV-2 patients, 614 (9.8%) were admitted to ICU and 677 (10.8%) died within 30 days. Among the 10 279 individuals hospitalized for influenza, 951 (9.2%) were admitted to ICU and 1275 (12.4%) died. The cohort of COVID-19 patients had a noticeably lower frequency of comorbidities compared with the cohort of influenza patients, except a similar prevalence of dementia in the COVID-19 cohort (Table 1). Furthermore, COVID-19 patients were slightly younger and had fewer filled prescriptions within the last 90 days compared with influenza patients. Among COVID-19 patients, 6.5% were registered with a hospital diagnosis for asthma and 8.5% with a chronic pulmonary disease (incl. COPD) diagnosis (Table 1). While 13.0% had filled a prescription for any inhaled pharmaceutical within the last 6 months (defined as usage), 10.3%, 8.3%, 8.1%, 0.9%, and 6.0% had used inhaled pharmaceutical containing corticosteroids (ICS), inhaled short-acting β_2-agonist (SABA), inhaled long-acting β_2-agonist (LABA), inhaled short-acting muscarinic antagonist (SAMA), or inhaled long-acting muscarinic antagonist (LAMA), respectively. Among influenza patients, 5.8% and 13.3% were registered with an asthma and a chronic pulmonary disease diagnosis, respectively. Any inhaled pharmaceutical use (26.9%) comprised ICS (18.7%), SABA (16.5%), LABA (13.3%), SAMA (2.3%), and LAMA (13.9%) use, respectively. In addition, a breakdown of ICS use by patient characteristics is reported in Table S2.

In our main analysis of COVID-19 patients, the 30-day hazard of admission to ICU was similar among ICS users compared with users of bronchodilators and not ICS (hazard ratio 1.09, 95% confidence interval [CI], 0.67–1.79; Table 2) and compared with all patients without ICS use (hazard ratio 1.17, 95% CI, 0.87–1.59; Table 2). For influenza patients, the 30-day hazard of admission to ICU was increased among ICS users compared with users of bronchodilators and not ICS (hazard ratio 1.43, 95% CI 0.89–2.30; Table 2), although not statistically significantly so. No large difference was observed among influenza patients when comparing ICS users with all patients without ICS use (hazard ratio 1.11, 95% CI 0.85–1.46; Table 2).

The 30-day hazard of death among COVID-19 patients was similar among ICS users compared with users of bronchodilators and not ICS (hazard ratio 0.78, 95% CI, 0.56–1.11; Table 2) and compared with all patients without ICS use (hazard ratio 1.02, 95% CI, 0.78–1.32; Table 2). For influenza patients, the 30-day hazard of death was similar among ICS users compared with users of bronchodilators and not ICS (hazard ratio 0.80, 95% CI, 0.63–1.01; Table 2) and compared with all patients without ICS use (hazard ratio 1.03, 95% CI, 0.87–1.22; Table 2). Furthermore, examining the 30-day hazard of mechanical ventilation or death, rather than admission to ICU or death, did not lead to different findings (Table S3).

Among all non-hospitalized individuals who tested positive for SARS-CoV-2, the 30-day hazard of hospitalization was increased in ICS users compared with all individuals with no ICS use (hazard ratio 1.59, 95% CI, 1.42–1.78; Table S4), but not compared with users of bronchodilators and not ICS. There was no association between ICS use and hospitalization in non-hospitalized individuals who tested

TABLE 1 Baseline characteristics of COVID-19 and influenza cohorts

Characteristic	COVID-19 (2020; $N = 6267$)	Influenza (2010–2018; $N = 10\,279$)
Age (median, 25th–75th percentile)	62 (47–77)	70 (58–80)
Female sex (%)	3023 (48.2)	5034 (49.0)
Comorbidities (%)		
Atrial fibrillation	639 (10.2)	1519 (14.8)
Asthma	410 (6.5)	774 (7.5)
Chronic pulmonary disease (incl. COPD)	534 (8.5)	2068 (20.1)
Dementia	166 (2.6)	292 (2.8)
Heart failure	371 (5.9)	1017 (9.9)
Hypertension	1483 (23.7)	3430 (33.4)
Inflammatory bowel disease	104 (1.7)	233 (2.3)
Malignancy	616 (9.8)	1529 (14.9)
Renal failure	667 (10.6)	1455 (14.2)
Charlson comorbidity index score (median, 25th–75th percentile)	0 (0–0)	0 (0 to 2)
≥5 asthma or COPD exacerbations within the latest 5 years	43 (0.7)	266 (2.6)
Pharmaceuticals		
Number of filled prescription within 90 days (median, 25th–75th percentile)	3 (1 to 6)	4 (2 to 8)
Use of inhaled pharmaceuticals (%)	814 (13.0)	2768 (26.9)
β2-agonists		
SABA	518 (8.3)	1700 (16.5)
LABA	507 (8.1)	1368 (13.3)
Corticosteroids	644 (10.3)	1925 (18.7)
Muscarinic receptor antagonists		
SAMA	58 (0.9)	232 (2.3)
LAMA	375 (6.0)	1425 (13.9)
Use of per oral corticosteroids (%)	366 (5.8)	1246 (12.1)

Note: Age, sex, comorbidities, and prescription drug use of the Danish cohorts of hospitalized individuals tested positive for SARS-CoV-2 during the COVID-19 epidemic, and individuals tested positive for influenza during 2010–2018, respectively.

positive for influenza, nor were there any associations between ICS use and death in non-hospitalized individuals who tested positive for influenza or SARS-CoV-2 during 2010–2018 and 2020, respectively.

Comparing the Nelson–Aalen cumulative hazard of death within 30-days in the COVID-19 cohort by exposure status, there was no noticeable difference between patients with filled prescriptions for inhaled corticosteroids compared with patients without filled prescriptions for inhaled corticosteroids (p-value for log-rank test, 0.23), with approximately 10% dying within 30 days (Figure 1(A)). In the influenza cohort, death was slightly more common among patients exposed to inhaled corticosteroids (p-value for log-rank test, 0.01) and approximately 10% died within 30 days (Figure 1(B)).

Examining the combined 30-day endpoint of admission to ICU or death by subtype of filled ICS, we observed a stronger reduction in risk among users of budesonide relative to users of fluticasone, compared with users of other inhaled pharmaceuticals and non-users of ICS in the COVID-19 cohort (Table S5). However, due to low statistical power we were not able to estimate hazard ratios by prescriptions of beclomethasone, ciclesonide, or mometasone.

In sensitivity analyses, we looked into the effect of inhaled corticosteroid use by excluding individuals with oral corticosteroid use within the last 6 months, different periods of the COVID-19 epidemic, different influenza seasons, persistency of ICS use, xanthines and leukotriene receptor antagonist use, and effects of prescriptions 2 weeks prior to a positive test (Tables S6–S11), and found no noticeable differences in the hazard of the combined endpoint in different subgroups. In addition, we considered if adjusting for the Charlson Comorbidity index score, beyond individual risk factors, might have led to over-adjustment of our estimates, but found no effect of omitting this factor (Table S12).

Finally, we investigated the 30-day hazard of death among patients admitted to ICU by use of inhaled corticosteroids (Table S13). In the COVID-19 cohort, we found no statistically significant difference in risk of death among ICU patients by usage of inhaled corticosteroids compared with users of bronchodilators but not ICS (hazard

TABLE 2 Relative risk of ICU admission and death within 30 days

ICS use comparison group	30-day relative risk of ICU admission Hazard ratio (95% CI)		30-day relative risk of death Hazard ratio (95% CI)	
	Crude[a]	Adjusted[b]	Crude[a]	Adjusted[b]
During COVID-19 epidemic[c]				
Patients with bronchodilator use	1.17 (0.72–1.91)	1.09 (0.67–1.79)	0.77 (0.55–1.09)	0.78 (0.56–1.11)
All patients without ICS use	1.19 (0.89–1.58)	1.17 (0.87–1.59)	1.15 (0.90–1.48)	1.02 (0.78–1.32)
During influenza epidemics[d]				
Patients with bronchodilator use	1.52 (0.95–2.43)	1.43 (0.89–2.30)	0.84 (0.66–1.06)	0.80 (0.63–1.01)
All patients without ICS use	1.22 (0.95–1.57)	1.11 (0.85–1.46)	1.24 (1.06–1.45)	1.03 (0.87–1.22)

Note: Hazard ratio of admission to intensive care unit (ICU) or death within 30 days, among patients with inhaled corticosteroid (ICS) use compared with patients without use of ICS, but use of inhaled β2-receptor agonist and/or muscarinic receptor antagonists, and compared with all patients without ICS use, in hospitalized test-positive individuals for COVID-19 (year 2020) or influenza (year 2010–2018), respectively.

[a]Adjusted only for age and sex.

[b]Furthermore adjusted for β2-receptor agonist use and muscarinic receptor antagonist use, in addition to the propensity score containing: atrial fibrillation, dementia, heart failure, hypertension, inflammatory bowel disease, malignancy, renal failure, Charlson Comorbidity index score, number of filled prescription within 90 days, and per oral corticosteroid use.

[c]During the COVID-19 epidemic 614 ICU admissions occurred, of which 69 were ICS users, 35 were users of bronchodilators, and 510 were patients without use of inhalers. Among non-ICU patients 563 deaths occurred, of which 70 were ICS users, 67 were users of bronchodilators, and 426 were patients without use of inhalers.

[d]During the 2010–2018 influenza epidemics 951 ICU admissions occurred, of which 224 were ICS users, 77 were users of bronchodilators, and 650 were patients without use of inhalers. Among non-ICU patients 915 deaths occurred, of which 199 were ICS users, 111 were users of bronchodilators, and 605 were patients without use of inhalers.

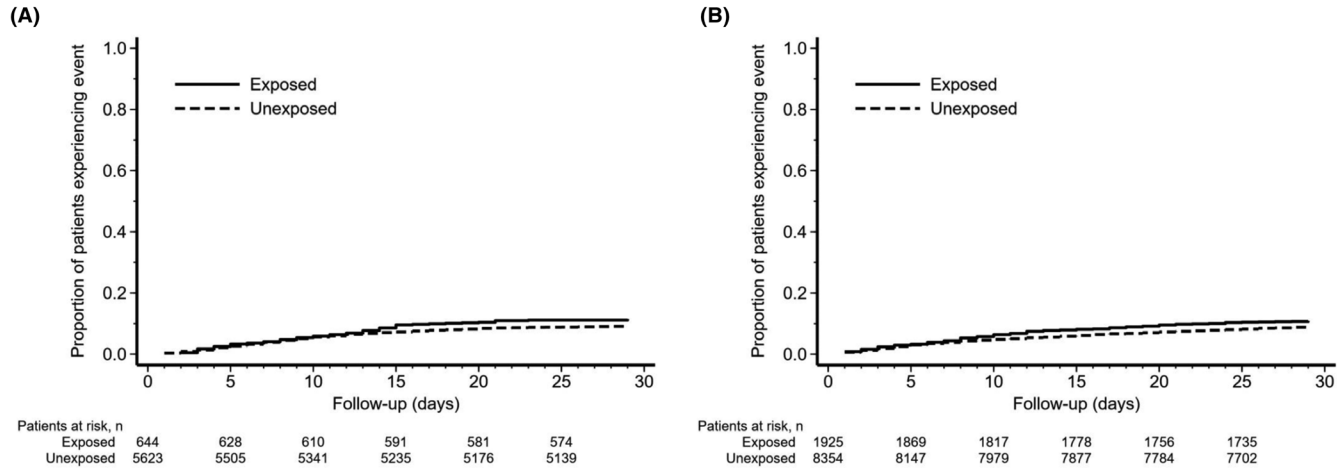

FIGURE 1 Cumulative hazard of death within 30 days. Nelson–Aalen cumulative hazard of death within 30 days, among inhaled corticosteroid (ICS) users (exposed) compared with all patients without ICS use (unexposed), in hospitalized test-positive individuals for SARS-CoV-2 (year 2020, panel A) or influenza (year 2010–2018, panel B), respectively

ratio 1.03 [95% CI, 0.45 to 2.36]) and all patients without ICS use (hazard ratio 1.40 [95% CI, 0.79–2.47]), equivalent to the influenza cohort, although the analysis was limited by low statistical power.

4 | DISCUSSION

In a large nationwide cohort of SARS-CoV-2 test-positive patients, we observed no statistically significant differences in COVID-19 outcomes between patients with inhaled corticosteroid use, patients with other inhaled pharmaceuticals (β_2-receptor agonist and/or muscarinic receptor antagonists) use, and all patients without inhaled corticosteroid use. Similarly, no consistent effects of inhaled corticosteroids on influenza outcomes during 2010–2018 were observed, which is in line with the results of randomized controlled trials of inhaled corticosteroid use and influenza,[14] lending credence to our results on COVID-19. Our findings therefore suggest no major adverse or beneficial effects of inhaled corticosteroid use in COVID-19.

Our results are overall in agreement with a large cohort study of COPD and asthma patients from the United Kingdom, which argues

for no increased risk of COVID-19-related death by prescription drug use of inhaled corticosteroids.[9] However, the study found a small increased risk of COVID-19-related death by inhaled corticosteroid use, which the authors speculated resulted from unmeasured confounding. Our study did not indicate an increased risk of death with inhaled corticosteroid use, in either crude or adjusted analyses, and benefitted from information on the entire population tested positive for SARS-CoV-2 and subsequently hospitalized (and vice versa), thereby virtually eliminating selection bias. Nevertheless, our supplementary analysis suggested an increased risk of hospital admission among ICS users compared with all individuals without use of ICS, but the association waned and was not significant when comparing with user of bronchodilators but not ICS, suggesting confounding by indication.

While our results are reassuring, we cannot rule out minor adverse or beneficial effects of inhaled corticosteroids on COVID-19 outcomes. Moreover, with regard to subtypes of inhaled corticosteroids, we found use of budesonide to be associated with a significant decreased risk of the combined end point of ICU admission or death. This result is in line with the recent randomized STOIC trial,[22] which found early administration of inhaled budesonide following a positive SARS-CoV-2 test to be result in a significant reduction of emergency department visits or hospitalization. The trial was nevertheless small ($n = 139$) and could therefore not assess effects on ICU admission rates or death.

Our cohort study included nationwide information on confirmed cases of SARS-CoV-2 infection and hospitalization in Denmark with negligible loss to follow-up and prospectively registered information on comorbidities and filled prescriptions prior to hospital admission. Furthermore, using hospitalized patients for our main analysis minimized potential selection bias due to potential differential SARS-CoV-2 testing in the general population. Having detailed information on ICS subtypes, persistency of ICS use, and per oral corticosteroid use, additionally allowed us to scrutinize the role of differential inhaled corticosteroids use. Nevertheless, we did not have information on drug dispensation during hospital admission. However, current medications are usually continued upon hospital admission and as nurses dispense medications while in-hospital, we only expect compliance to current medications to be higher during hospitalization.

We did not have information on smoking status and body mass index (BMI) which potentially could have confounded the association between inhaled corticosteroids use and disease outcomes. However, smoking and BMI would have confounded both the analysis of the COVID-19 epidemic and the influenza epidemics, why the confounding impact of smoking and BMI is likely to negligible given similar results of our study and randomized controlled trials of ICS and influenza, showing no effect of ICS on influenza morbidity. A further advantage of our study was the ability to compare morbidity of COVID-19 with historical influenza morbidity, as both are viral diseases with principal manifestations in the respiratory system. Hypothetically, there could be chronology bias, as we are investigating effects of ICS use in 2010–2018 and 2020, respectively, but we have no reason to believe there are major differences in population ICS use between the two time periods. We found similar effects of inhaled corticosteroid use on COVID-19 morbidity in 2020 and influenza morbidity during 2010–2018. The finding of no effect of inhaled corticosteroids on influenza was consistent with a meta-analysis on randomized controlled trials of inhaled corticosteroid treatment.[14] Furthermore, in parallel with other reports we found COVID-19 to be associated with a markedly high level of overall morbidity and mortality compared with influenza.[23,24] This finding underscores the severity of COVID-19, since our COVID-19 cohort was both younger and generally healthier than our influenza cohort was.

Together with the findings of others, our study supports continued use of inhaled corticosteroid according to current guidelines. Although suggesting no major adverse or beneficial effect of inhaled corticosteroids on COVID-19, our study is no substitution for randomized controlled trials of inhaled corticosteroids in the treatment of COVID-19. As also suggested by others,[25] inhaled corticosteroids could potentially limit both short-term and long-term COVID-19 morbidity and the STOIC trial suggest marked benefits with early treatment. However, larger trials are needed to assess effects on severe outcomes.

Taken together, our study found no effect of inhaled corticosteroids on COVID-19 morbidity or mortality compared with either users of bronchodilators only or all patients without inhaled corticosteroid use overall. Treatment with inhaled corticosteroids should therefore follow current guidelines, unless investigated in randomized controlled trials under the supervision of medical professionals.

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CONFLICT OF INTEREST

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ETHICS STATEMENT

As the study was based on de-identified information from the Danish national registers and as study participants are never contacted, consent from the Danish research bioethics committees are not required. The study's use of register data was covered by the approval from The Danish Medicines Agency given to A.P.

AUTHOR CONTRIBUTIONS

Data: Anton Pottegård had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design*: Anders Husby and Anton Pottegård. *Acquisition, analysis, or interpretation of data*: All authors. *Drafting of manuscript*: Husby. *Critical revision of the manuscript for important intellectual content*: Anton Pottegård and Anders Hviid. *Statistical analysis*: All authors. *Administrative, technical, or material support*: Anders Husby and Anton Pottegård. *Supervision*: Anton Pottegård and Anders Hviid.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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