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The Impact of Social Distancing in 2020 on Admission Rates for Exacerbations in Asthma: A Nationwide Cohort Study



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What is already known about this topic? Social distancing measures introduced during the coronavirus disease 2019 pandemic have reduced admission rates for various infectious and noninfectious respiratory diseases; however, its impact on asthma exacerbation rates remains to be explored.

What does this article add to our knowledge? Our national-level cohort study following 38,225 patients with asthma showed that there was a significant gradual decline in exacerbation rates following the national lockdown, when assessing both hospital admission and out-of-hospital exacerbations.

How does this study impact current management guidelines? Although the extensive social distancing measures are clearly too comprehensive to routinely advise to patients with asthma, our results suggest that patients with asthma should be encouraged to follow basic hygiene principles whenever possible.

BACKGROUND: Social distancing measures introduced during the coronavirus disease 2019 pandemic have reduced admission rates for various infectious and noninfectious respiratory diseases. We hypothesized that rates of asthma exacerbations would decline following the national lockdown in Denmark. **OBJECTIVE:** To determine weekly rates of in- and out-of-hospital asthma exacerbations before and during the social distancing intervention implemented on March 12, 2020. **METHODS:** All individuals older than 18 years with at least 1 outpatient hospital contact with asthma as the main diagnosis from January 1, 2013, to December 31, 2017, were included. Weekly asthma exacerbation rates from January 1, 2018, to May 22, 2020, were calculated. An interrupted time-series model with the lockdown on March 12, 2020, as the point of interruption was used. **RESULTS:** A total of 38,225 patients with asthma were identified. The interrupted time-series model showed no

immediate fall in exacerbation rates during the first week after March 12, 2020. However, there was a significant decline in weekly exacerbation rates in the following 10 weeks (change in trend for exacerbations requiring hospitalization: -0.75 [95% CI, -1.39 to -0.12]; $P < .02$ and in all asthma exacerbations: -12.2 [95% CI, -19.1 to -5.4 ; $P < .001$), amounting to a reduction of approximately 1 and 16.5 exacerbations per year per 100 patients in the cohort, respectively. **CONCLUSIONS:** The introduction of the social distancing measures in Denmark did not lead to an immediate reduction in asthma exacerbation rates; however, a gradual decline in exacerbation rates during the following 10-week period was observed. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:2086-92)

Key words: Asthma; Exacerbations; Epidemiology; Lockdown; Social distancing

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Abbreviations used

COPD- chronic obstructive pulmonary disease
COVID-19- coronavirus disease 2019
ITS- interrupted time-series

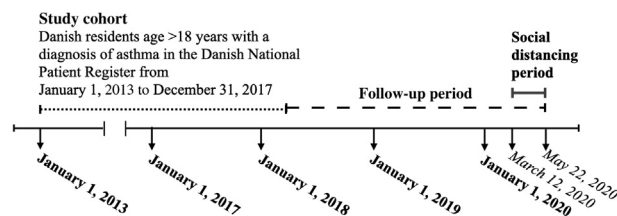


FIGURE 1. Inclusion and timeline.

INTRODUCTION

Asthma affects an estimated 315 million people worldwide,¹ and despite currently available highly effective treatment regimes, 20% to 40% of patients experience at least 1 acute exacerbation every year.^{2,3} Consequently, research in pharmacological and nonpharmacological strategies to reduce the risk of acute exacerbations in asthma is much warranted.

Social distancing measures introduced during the coronavirus disease 2019 (COVID-19) pandemic have reduced admission rates for respiratory tract infections.^{4,5} Because viral airway infections have been associated with up to 80% of acute exacerbations in asthma,^{6,7} it has been hypothesized that the social distancing measures introduced during the pandemic would lead to an overall decline in asthma exacerbations.

Earlier studies have reported reduced hospital admission rates for asthma exacerbations during the period in which the social distancing measures were implemented.^{8,9} However, it is important to take into account that in this period, a significant reduction in health care utilization among patients with chronic diseases was observed, explained by a reduced availability of health care services due to the lockdown and possibly also due to patients' fear of contracting the infection while leaving their houses.^{10,11} Therefore, when aiming to establish the effects of social distancing measures on incidences of asthma exacerbations, it is crucial to evaluate both in- and out-of-hospital exacerbations because the observed number of hospital admissions may underestimate the true number of incident asthma exacerbations.

Using data from the Danish nationwide health registers, we aimed to identify weekly incidence rates of asthma exacerbations, including in- and out-of-hospital exacerbations, and compare incidence rates during the social distancing period to the expected incidence rates based on interrupted time-series (ITS) analyses using data from the 2 previous years.

METHODS

Study design

The study is a retrospective cohort study using data from the Danish nationwide health registers. Data analyses began June 1, 2021, after receiving access to data from the national health administrative registries.

Ethical approval

The study has been approved by the Danish Data Protection Agency (journal no. P-2020-989). In Denmark, retrospective use of registry data does not require ethical approval or patient consent.

Cohort

The cohort was defined as follows: all Danish inhabitants older than 18 years by January 1, 2018, with at least 1 outpatient hospital contact with asthma as the main diagnosis registered in the Danish National Patient Register during the period January 1, 2013, to December 31, 2017 (inclusion period). The day of the first

outpatient visit during the inclusion period was defined as the inclusion date (Figure 1). Patients were excluded from the cohort if they had had a diagnosis of COVID-19, defined as a positive COVID-19 test result during the follow-up period (January 1, 2018, to May 22, 2020). The presence of a positive PCR test result for severe acute respiratory syndrome coronavirus 2 was confirmed by the COVID-19 surveillance data from the Danish Microbiology Database and Statens Serum Institute.

Data sources

At date of birth or immigration to the country, all Danish citizens receive a unique personal identification number in the Civil Registration System. We used this personal identification number for exact linkage on an individual level between registers, ensuring complete follow-up.

The following nationwide registers were used:

1. The National Prescription Register¹²: Holds information on all prescriptions dispensed from Danish pharmacies since 2004 coded according to the Anatomical Therapeutic Chemical classification system.
2. The Danish Central Personal Register: Holds information on citizens of Denmark including vital status, sex, and date of birth.
3. The Danish National Patient Register¹³: Holds information on all admissions to Danish hospitals since 1977 and hospital outpatient visits since 1995. Each hospital visit is coded by physicians with a primary diagnosis and, if relevant, 1 or more secondary diagnoses according to the *International Classification of Diseases, 10th revision* from 1994.¹⁴ It does not include information from primary care consultations.
4. COVID-19 surveillance database of Statens Serum Institut (the Danish center for control of infectious diseases and biological threats).

Definition of outcomes

The cohort was followed for outcomes from January 1, 2018, through May 22, 2020. The time period of national lockdown was defined as the period from March 12 to May 22, 2020, because this was considered the period with the most extensive lockdown restrictions in Denmark during the COVID-19 pandemic. No social distancing measures were introduced or law enforced before this period, whereas the period after May 22, 2020, was dominated by alternating social distancing measures and a general reduction in lockdown restrictions. The timeline of the introduction of the social distancing measurement is presented in Table I and described in detail in this article's Online Repository at www.jaci-inpractice.org.

The outcomes of interest were defined as follows:

1. Weekly incidences of asthma exacerbations requiring hospitalization defined as acute hospital admissions or emergency room visits with asthma as the primary diagnosis (*International*

TABLE I. Timeline of introduction of the social distancing measures in Denmark in March 2020

Date	Social distancing measures implemented
March 12, 2020	All secondary schools and higher education institutions were closed. A ban was introduced on gatherings of more than 100 persons. The borders were closed for non-Danish citizens. Masks were not mandatory ¹⁵
March 16, 2020	All primary schools, day-care centers, and similar places were closed
March 18, 2020	The national ban on any gathering was further restricted from 100 to 10 people. All shopping centers and stores with close contact such as hairdressers and nightclubs were closed ¹⁶
April 5, 2020	Phase 1 of the reopening was introduced. Day-care institutions and primary schools from 0 to fifth grade were opened
April 15, 2020	Upper secondary education institutions for graduating students were reopened
May 8, 2020	Phase 2 of the reopening started. Malls and outdoor sport facilities reopened but under certain precautions of continued social distancing
May 22, 2020	Restaurants, cafés, bars, and the entire primary school reopened through May 18 to May 25 under certain precautions of continued social distancing

Classification of Diseases, 10th revision code J45 [asthma] or J46 [status asthmaticus]) lasting more than 24 hours during the period from January 1, 2018, to May 22, 2020.

- Weekly incidences of all asthma exacerbations, including both outpatient visits and exacerbations requiring hospitalization from January 1, 2018, to May 22, 2020. An out-of-hospital exacerbation was defined as an asthma exacerbation requiring redemption of a course of oral corticosteroids (doses of 25-50 mg daily for 5-14 days). Near the end of 2018 and the beginning of 2019, there was a substantial but temporary national shortage of prednisolone 25-mg tablets, leading to a sharp decrease in the number of these prescriptions (S. H. Pedersen, Danish Medicines Agency, personal communication, January 21, 2021). Because we do not believe this decrease represents a change in exacerbation rate, we excluded the 5-week period running from December 12, 2018, to January 17, 2019, from the data set.
- Cumulated incidences of asthma exacerbations requiring intensive care unit admission from March 12 to May 22, 2020, compared with the same period in 2018 and 2019.

Statistical analysis

For descriptive statistics, categorical variables were presented as frequencies and proportions, and continuous variables as median values and interquartile ranges.

For sensitivity, we fitted a controlled ITS model to the weekly incidences in 2020, with the incidences of 2018 and 2019 as the control. With the ITS model, 2 potential changes that could occur because of the intervention were assessed: the change in level and the change in trend. Change in level corresponds to a possible sudden change in exacerbation rate immediately at the onset of the intervention (social distancing period) and is defined as 0 until the intervention and then 1 throughout the intervention period. A change in trend corresponds to difference in the trend (slow change in exacerbation rate over time) between preintervention and postintervention periods. We fitted the data with a seasonal autoregressive integrated moving average model with 2 external regressors. We used the “auto.arima” function in the “forecast” package in R to get an initial estimate of the orders of the model. We then manually adapted the model on the basis of residual plot until we obtained the best fit. The method is described in detail by Schaffer et al.¹⁵

Statistical analyses were performed using SAS 9.4 through Studio 3.71 (SAS Institute Inc, Cary, NC) and R version

4.0.4 (2021-02-15; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Cohort

Of the 38,225 patients with asthma identified (61% women, most aged 45-74 years) (Table II and Figure 2), 6562 patients (17.1%) had at least 1 exacerbation during the follow-up period from January 1, 2018, through May 22, 2020.

Exacerbations during follow-up

During the social distancing period (March 12 to May 22, 2020), a total of 948 exacerbation episodes were experienced by 900 patients (2.4% of the total cohort). Of these episodes, 71 (7%) required hospitalization. During the corresponding period of the year before (March 12 to May 22, 2019), a total of 1094 exacerbation episodes were experienced by 1041 patients (2.9% of the total cohort). Of these episodes, 85 (8%) required hospitalization. During the corresponding period in 2018, a total of 1227 exacerbations were experienced by 1169 patients (3.1% of the total cohort). Of the 1227 exacerbations, 88 (7%) required hospitalization.

The exacerbation rates for every week during the entire follow-up period (March 4, 2019, to May 22, 2020) are presented in Figure 3, A and B. Figure 3, A, shows weekly incidences of exacerbations requiring hospitalization, whereas Figure 3, B, shows weekly incidences of all exacerbations.

There was no difference in change in exacerbation rates following the introduction of the social distancing measures across age groups (see Figure E1, A and B, in this article's Online Repository at www.jaci-inpractice.org), or when comparing patients with high inhaled corticosteroid use, defined as daily inhaled corticosteroid use above the median, with those with low- or no inhaled corticosteroid use (Figure E1, A and B).

During the social distancing period, a total of 4 intensive care unit admissions due to asthma were registered. During the same period in 2018 and 2019, a total of 3 and 7 intensive care unit admissions due to asthma were registered, respectively.

ITS analyses

For sensitivity analysis, we used an ITS model to assess the effect of the social distancing measures on exacerbation rates. We hypothesized that the onset of social distancing measures would cause an immediate change in the level of exacerbations (=

TABLE II. Baseline characteristics

Characteristic	Cohort n = 38,225
Age group, n (%) [*]	
18-24	3813 (10)
25-34	4986 (13)
35-44	5910 (16)
45-54	7288 (19)
55-64	6822 (18)
65-74	6134 (16)
≥75	3272 (9)
Sex: female, n (%)	23,443 (61)
Asthma medication, n (%) [†]	
Use of inhaled corticosteroid (ICS) as monotherapy [‡]	8406 (22)
Use of ICS <i>plus</i> long-acting β ₂ -agonist (LABA) [‡]	21,766 (57)
Use of any ICS [‡]	30,172 (79)
Median daily ICS dose (budesonide equivalents) (μg) (25%-75% quartiles) [§]	316 (158-526)
Any LABA [‡]	23,233 (61)
Short-acting β ₂ -agonist [‡]	17,283 (45)
Leukotriene antagonists [‡]	5304 (14)
Long-acting muscarinic antagonist [‡]	6049 (16)
Daily use of oral corticosteroid (2.5-5 mg/d) [‡]	871 (2)

^{*}By January 1, 2018.

[†]Based on prescriptions redeemed from January 1 to December 31, 2019.

[‡]At least 1 redeemed prescription.

[§]In patients who were using ICSs.

change in level) as well as a change in the long-term trend, which would be seen as a slower and more gradual decline in the weekly exacerbation rates (= change in trend).

When assessing the effects of introducing the social distancing measures on hospitalization rates for asthma exacerbation, the model showed no significant changes in level (2.3 [95% CI, -2.0 to 6.7], $P = .30$), whereas a significant reduction in trend was observed (-0.75 [95% CI, -1.39 to -0.12], $P < .02$) (Fig 4, A). At the end of the 10 weeks of social distancing measures, this decrease amounted to approximately 1 exacerbation per year per 100 patients in the cohort.

When assessing the effects of the social distancing measures on the overall weekly exacerbation rates, a significant increase was observed in level (59.1 [95% CI, 12.5 to 105.7], $P = .01$) following the introduction of the social distancing measures (Fig 4, B). The long-term trend, however, showed a significant decrease in exacerbation rates (-12.2 [95% CI, -19.1 to -5.4], $P < .001$) after the onset of social distancing. After the 10-week lockdown period, this change in trend amounts to a reduction of 16.5 exacerbations per year per 100 patients in the cohort. When visually inspecting the graph (Figure 4, B), the increase in level seems to be caused mostly by a high incidence of exacerbations in the single week following the introduction of social distancing. To see the effect of the increase in exacerbation rate this single week, we also fitted the model to the data set with the exacerbation rate of the first week of lockdown imputed to the value of the week before (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org). This changed the result so that no significant change to the level was observed (25.6 [95% CI,

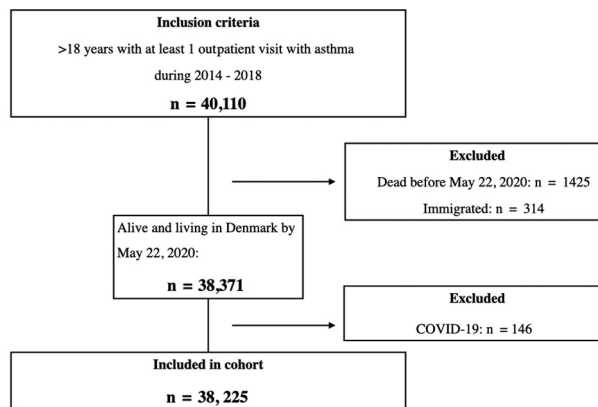


FIGURE 2. Flow chart of study identification, inclusion and exclusion criteria.

-17.4 to -68.7], $P = .24$), whereas the decrease in trend remained significant (-8.0 [95% CI, -14.4 to -1.6], $P = .01$).

DISCUSSION

Using nationwide health registers, we found a significant gradual decline in the rate of asthma exacerbations requiring hospitalization as well as overall asthma exacerbation rates during the 10 weeks following the introduction of the social distancing measures. Because viral respiratory infections are known to cause many asthma exacerbations, this gradual decline may represent a general decline in the level of respiratory infections in society, gradually lowering infection rates.

Surprisingly, we observed an immediate *increase* in the level of overall exacerbation rates in the first week following the introduction of the social distancing measurements. This immediate increase can be explained entirely by a very high number of out-of-hospital exacerbations in the first week of lockdown, which increased to 191, compared with 133 the week before. We cannot decipher the precise cause of this peak, which can be incidental or caused by some infection spreading throughout society, which was then abruptly hindered by the onset of social distancing with 1 week of latency, or it could be explained by undiagnosed COVID infections. Another possible explanation is that patients were afraid of supply issues and stockpiled prednisolone, which we then falsely interpret as an increase in exacerbation rates. Indeed, stockpiling of respiratory medicine in the beginning of the COVID-19 pandemic was reported from the National Health Service.¹⁶ Overall, we find it unlikely that this apparent increase is explained by a direct increase in exacerbations caused by the introduction of the social distancing measures.

When assessing the effects of the introduction of the social distancing measures on hospitalization rates and on overall exacerbation rates, the decreases amounted to approximately 1 and 16.5 exacerbations per year per 100 patients in the cohort, respectively, which we consider a modest effect size if compared with, for example, the effects of biologic therapies on asthma exacerbation rates.¹⁷⁻¹⁹ However, it must be noted that in such a comparison, study populations are not comparable, because the study populations in most studies of biological treatments are "enriched" with patients with frequent exacerbations, which is

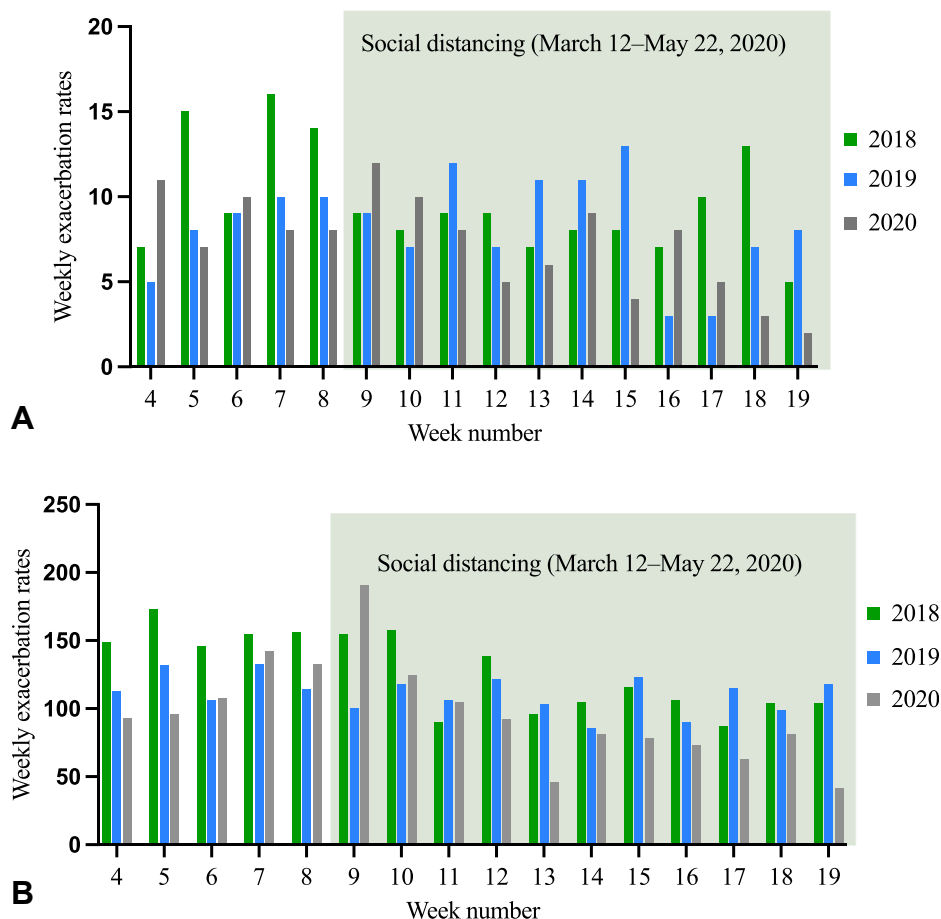


FIGURE 3. (A) Weekly incidences of asthma exacerbations requiring hospitalization from week 4 to 19 in 2018, 2019, and 2020. (B) Weekly incidences of overall asthma exacerbation rates including both in- and out-of-hospital exacerbations from week 4 to 19 in 2018, 2019, and 2020.

not the case in our real-life cohort. Unfortunately, we are not able to get reliable data on the exacerbation history of patients in our cohort, because a large part of patients entered the cohort at their very first visit to the outpatient clinic where they were diagnosed with asthma, and therefore had no prior history of exacerbations. Thus, we are not able to make subanalyses on patients with frequent exacerbations.

Our results are overall in line with findings from a recent cohort study from England²⁰ that reported a significant reduction in asthma exacerbation rates following the national lockdown. Yet, in contrast to our findings, the reduction was seen in only those exacerbations that resolved within primary care. A possible explanation for this can be that the authors counted emergency department visits as hospitalizations, whereas hospitalizations in our study were defined as a hospital stay lasting more than 24 hours. The observed effect size of the social distancing measures on exacerbation rates was also larger than in our study. Reasons for this may include differences in national lockdown strategies between Denmark and England, as well as the fact that only those patients who were older than 18 years were included in our cohort, whereas the English cohort also included pediatric patients. Previous studies have suggested that exacerbations in asthma are more

often caused by viral infections in children with asthma when compared with adult patients with asthma.^{6,21,22} Thereby, it is likely that the social distancing measures would impact a mixed-aged cohort greater than an adults-only cohort. Last, it shall be noted that Shah et al,²⁰ unlike us, did not observe an increase in overall exacerbation rates immediately following the introduction of the social distancing measures, which could support that our finding on this is more likely to have other explanations as discussed above.

In patients with chronic obstructive pulmonary disease (COPD), a significant reduction in exacerbation rates following the introduction of the social distancing measures has been reported.^{23,24} Saeed et al²⁴ found a 50% reduction in exacerbation rates among patients with severe and very severe COPD following the introduction of the social distancing measures. This effect size is considerably larger than what we observed in our present asthma cohort. There are several potential explanations for this seeming discrepancy. First, it can be caused by differences in patients' adherence to the social distancing measures, with the patients with COPD being more adherent when compared with the patients with asthma. Second, patients in the COPD cohort all had severe and very severe diseases and were thus considerably more vulnerable to viral infections and more likely to benefit

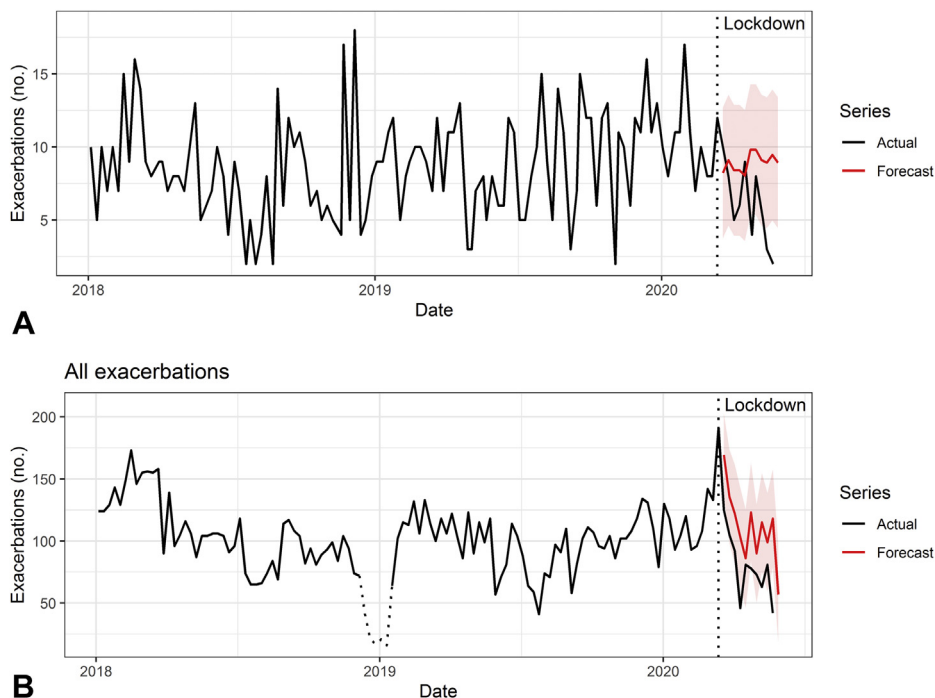


FIGURE 4. (A) Weekly rates of asthma exacerbations requiring hospitalization. (B) Weekly rates for all asthma exacerbations, both in- and out-of-hospital. The 5-week period running from December 12, 2018, to January 17, 2019, was removed from the data set (dotted line) because of a substantial but temporary national shortage of prednisolone 25-mg tablets. The red line indicates expected exacerbation rates based on the ITS analysis, and the black line shows actual exacerbation rates. The light red area is the 95% CI.

from extensive social distancing measures. Lastly, given the distinct and diverse nature of COPD and asthma, the complex interaction between exo- and endogen factors, which in the end leads to exacerbations, is not identical.

The main strength of our study is that we were able to use nationwide health registers, ensuring complete follow-up on all included patients. Furthermore, the inclusion criteria ensured that the asthma diagnoses had been verified by respiratory physicians on the basis of clinical assessment and testing, ensuring the validity of the diagnosis. Second, we assessed both in- and out-of-hospital exacerbations. It can be speculated whether the threshold for referring patients for hospital treatment was different during the peak of the COVID-19 pandemic due to limited resources in the hospitals as well as patients' fear of catching the virus during a hospital stay. Indeed, medical consultation pattern changed dramatically during the pandemic from face-to-face consultations to telephone, email, or virtual consultation.¹⁶ If and how this has affected prescribing rates of courses of oral corticosteroids for patients with asthma as well as hospital referrals are speculative; however, it is likely that caregivers would be more liberal with prescribing courses of oral corticosteroids as well as referring patients for hospital evaluation, if they were unable to call patients in for clinical assessment. If this was the case, our results would underestimate the effects of the social distancing measures.

When evaluating prescription pattern for asthma inhalers, data from the National Health Service have shown that prescription redemptions of asthma inhalers increased significantly during the

beginning of the pandemic, with a peak demand in March 2020.¹⁶ Even though this could also reflect stockpiling, data from electronic recordings from the Propeller Health (Madison, Wis), a digital platform that tracks inhaler use through electronic medication monitors, supports that adherence to prophylactic asthma medicine increased during the beginning of the pandemic.²⁵ As poor adherence to inhaler medicine is a huge challenge for many patients with asthma, and one of the main factors that lead to exacerbations,²⁶ increased adherence could constitute part of the explanation for the reduction in exacerbation rates observed in our study.

Our definition for an asthma exacerbation was the need for oral corticosteroids of 25 to 50 mg daily for 5 to 14 days, because this is the national treatment recommendation from the Danish Society of Respiratory Medicine.²⁷ It can be argued whether the definition should be broadened out, for example, to include down to 3-day courses of oral corticosteroids. However, because the Danish Asthma Treatment Guidelines do not recommend this short treatment duration, we believe that any observed outcomes based on treatment durations less than 5 days would represent events other than asthma exacerbations.

Although our study has several strengths, the following limitations deserve careful consideration. First, our analyses were based on nationwide registers, which do not contain information on adherence to the social distancing interventions, for example, through questionnaires, which could have led to both overestimation and underestimation of the effect of social distancing. Second, the social distancing intervention is a composite of

several initiatives, and as such, we are unable to determine which of the initiatives mostly affected the risk estimates with social distancing. Furthermore, it is difficult to distinguish the exact impact on outcomes of the initiation of the phase 1 reopening on April 5. However, when evaluating transmission rates for severe acute respiratory syndrome coronavirus 2 in Denmark following the phase 1 of the reopening, the transmission rates did not increase in the following month,²⁸ probably because the overall social distancing measures were still widespread throughout society at the time. So even though the social distancing measures were less constrained after April 5, the immediate effect of this early reopening on exacerbation rates is likely to have been limited, which our results also suggest.

CONCLUSIONS

We observed a moderate trend toward a reduction in asthma exacerbation rates following the national lockdown introduced on March 12, 2020, while evaluating the overall number of in- and out-of-hospital exacerbations. Although the extensive social distancing measures are clearly too comprehensive to routinely advise to patients with asthma, our results suggest that patients with asthma should be encouraged to follow basic hygiene principles whenever possible.

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ONLINE REPOSITORY

TIMELINE FOR THE INTRODUCTION OF THE SOCIAL DISTANCING MEASURES IN DENMARK IN MARCH 2020

March 12: All secondary schools and higher education institutions were closed and all public-sector employees not having critical functions were sent home. In the private sector, employers were urged by the authorities to allow their employees to stay home. Malls and all indoor public cultural institutions, libraries, and indoor leisure facilities were closed, and a ban was introduced on gatherings of more than 100 persons together. The Danish borders were closed for every non-Danish citizen. Outings were not under any restrictions. Masks were not mandatory.^{E1}

March 16: All primary schools, day-care centers, and similar places were closed. The municipalities established limited day-

care for children if their parents could not stay home and take care of them.

March 18: The assembly ban was restricted from 100 to 10 people. All shopping centers and stores with close contact such as hairdressers and nightclubs were closed, and restaurants were only allowed to serve take-out. Breaking the restrictions was associated with fines, and public areas were controlled by police officers.^{E2}

April 5: Phase 1 of the reopening was introduced. Day-care institutions and primary schools from 0 to fifth grade were opened.

April 15: Upper secondary education institutions for graduating students were reopened.

May 8: Phase 2 of the reopening started. Malls and outdoor sport facilities reopened but under certain precautions of continued social distancing.

May 18: Restaurants, cafés, bars, and primary schools reopened through May 18 to May 25 under certain precautions of continued social distancing.

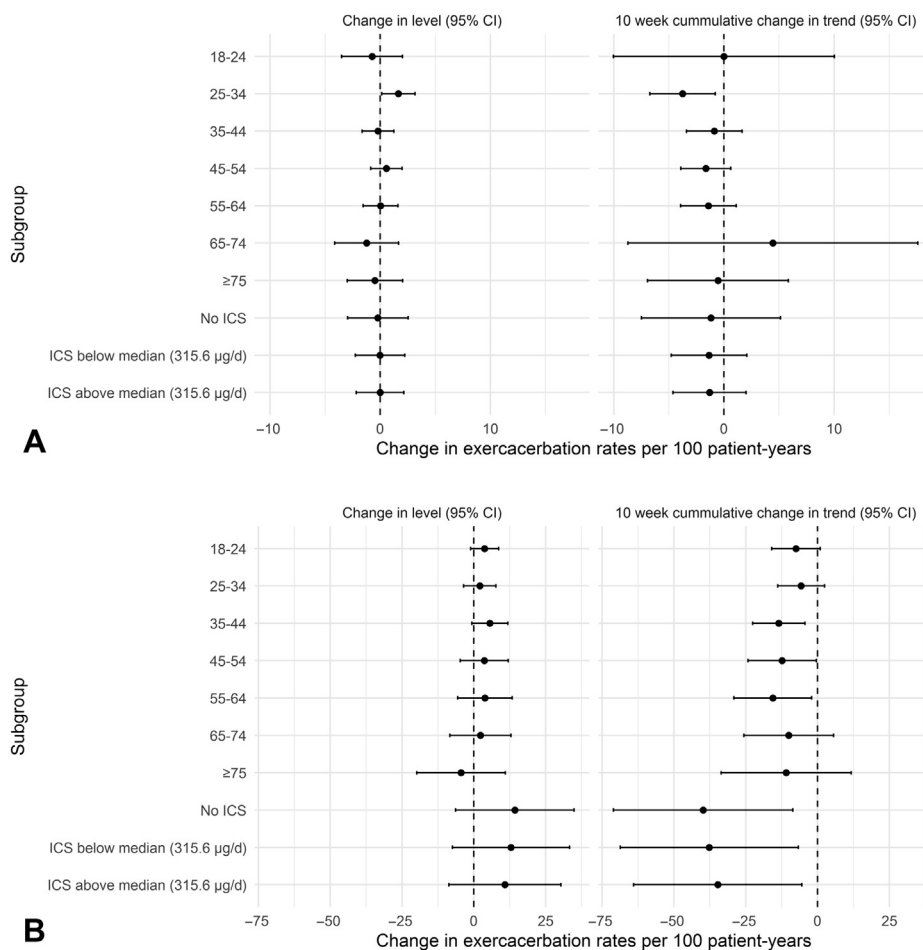


FIGURE E1. (A) Change in exacerbation rates after onset of social distancing for exacerbations requiring hospitalizations across age groups and daily ICS doses (change in exacerbation rates per 100 patient-years.) (B) Change in exacerbation rates after onset of social distancing for all exacerbations, both in- and out-of-hospital across age groups and daily ICS doses (change in exacerbation rates per 100 patient-years.) Level is the immediate change after onset of social distancing, whereas trend is the cumulative weekly change after 10 weeks of lockdown. *ICS*, Inhaled corticosteroid.

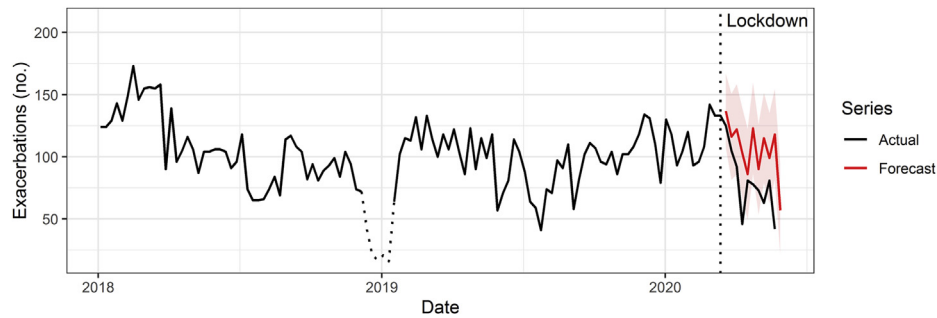


FIGURE E2. Weekly rates for all asthma exacerbations, both in- and out-of-hospital. The 5-week period running from December 12, 2018, to January 17, 2019, was removed from the data set (dotted line) because of a substantial but temporary national shortage of prednisolone 25-mg tablets. The red line indicates expected exacerbation rates based on the ITS analysis, and the black line shows actual exacerbation rates. The light red area is the 95% CI. The model is fitted to the data set, with the exacerbation rate of the first week of lockdown imputed to the value of the week before.

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