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Original Contribution

Social Distancing in Relation to Severe Exacerbations of Chronic Obstructive Pulmonary Disease: A Nationwide Semi-Experimental Study During the COVID-19 Pandemic

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Social distancing measures introduced on March 12, 2020, in Denmark during the COVID-19 pandemic may affect non–COVID-19 admissions for severe acute exacerbation of chronic obstructive pulmonary disease (s-AECOPD). We compared rates of s-AECOPD in a nationwide, observational, semi-experimental cohort study using data from all Danish inhabitants between calendar week 1 through 25 in 2019 and 2020. In a sub-cohort of patients with chronic obstructive pulmonary disease, we examined incidence of s-AECOPD, admissions to an intensive care unit, and all-cause mortality. A total of 3.0 million inhabitants aged ≥40 years, corresponding to 3.0 million person-years, were followed for s-AECOPD. In the social distancing period in 2020, there were 6,212 incidents of s-AECOPD, compared with 11,260 incidents in 2019, resulting in a 45% relative risk reduction. In the cohort with chronic obstructive pulmonary disease ($n = 16{,}675$), we observed a lower risk of s-AECOPD in the social distancing period (subdistribution hazard ratio (HR) = 0.34, 95% confidence interval (CI): 0.33, 0.36; absolute risk: 25.4% in 2020 and 42.8% in 2019). The risk of admissions to an intensive care unit was reduced (subdistribution HR = 0.64, 95% CI: 0.47, 0.87), as was all-cause mortality (HR = 0.83, 95% CI: 0.76, 0.90). Overall, the social distancing period was associated with a significant risk reduction for hospital admittance with s-AECOPD.

chronic obstructive pulmonary disease; clinical epidemiology; cohort study; COPD exacerbations; respiratory infections; social distancing

Abbreviations: AECOPD, acute exacerbations of chronic obstructive pulmonary disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DrCOPD, Danish Register of Chronic Obstructive Pulmonary Disease; DNPR, Danish National Patient Register; HR, hazard ratio; ICU, intensive care unit; IRR, incidence rate ratio; s-AECOPD, severe acute exacerbations of chronic obstructive pulmonary disease.

Chronic obstructive pulmonary disease (COPD) is, in the majority of cases, a preventable disease accounting for almost 5% of all deaths worldwide (1). Acute exacerbations of COPD (AECOPD) are associated with subsequent increased rates of morbidity and mortality. Consequently, research in pharmacological and nonpharmacological interventions remain focused on strategies to reduce the risk of AECOPD (2–5).

Social distancing is a community mitigation measure that is aimed to reduce the transmission of microbes by increasing physical distance and reducing close contact (6). Modeling studies have shown that workplace social distancing measures may reduce the cumulative seasonal influenza infection rate by 23% in the general population (7) and that a combined intervention consisting of quarantine, school closure, and workplace distancing could reduce SARS-CoV-2 infections by >78% (8). Globally, there are no systematic data, to our knowledge, on the effect of social distancing on the risk of AECOPD requiring hospitalization (i.e., severe AECOPD (s-AECOPD). Social distancing was introduced

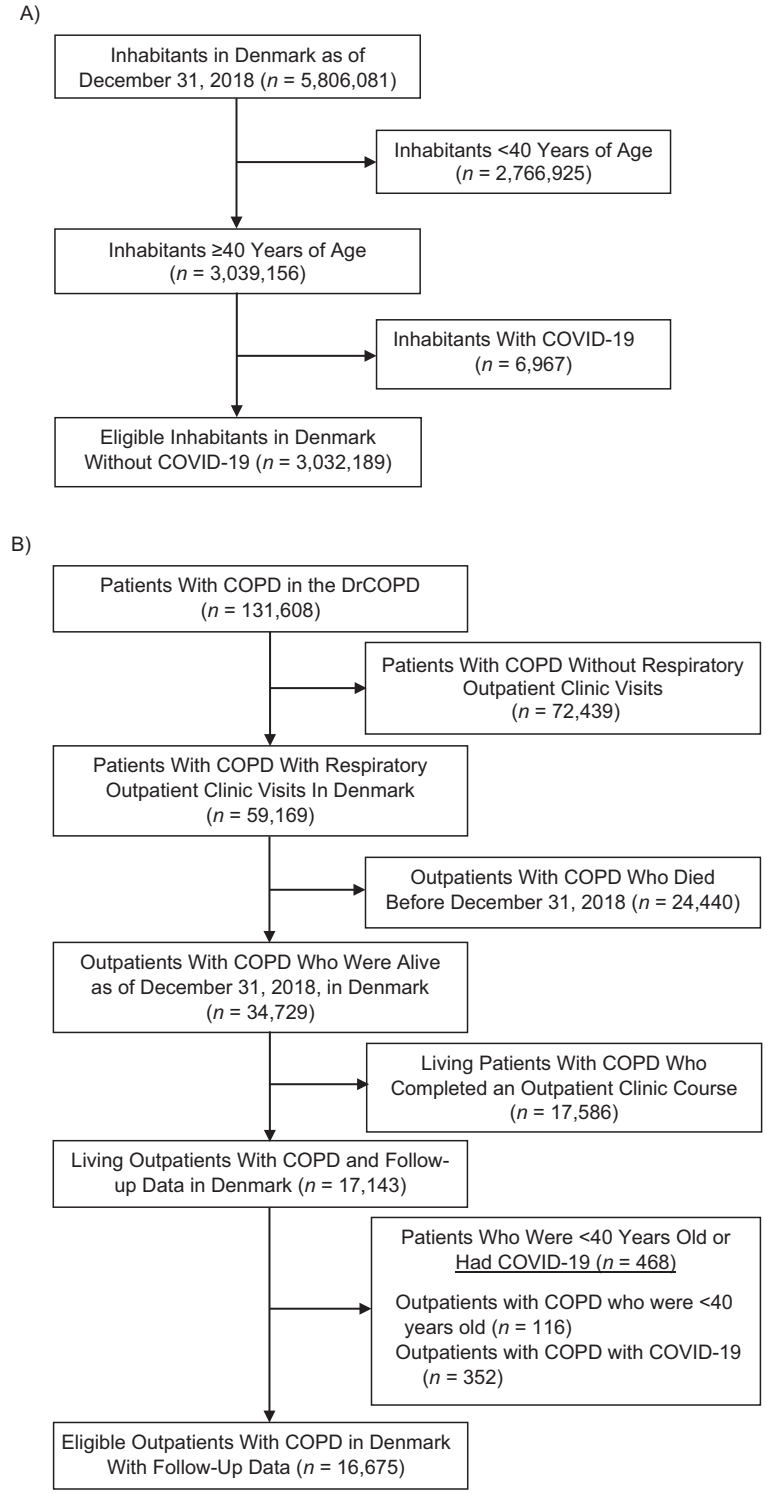

Figure 1. Study flowchart for the main cohort and the chronic obstructive pulmonary disease (COPD) cohort, Denmark, 2019–2020. A) Selection of study population for the main cohort of 3,032,189 eligible inhabitants in Denmark registered in the Danish National Patient Register and alive as of December 31, 2018. B) Selection of COPD cohort of 16,675 eligible patients with specialist-verified COPD, registered with COPD in the DrCOPD, alive as of December 31, 2018, and with follow-up data in 2019 and 2020, if not dead. DrCOPD, Danish Register for Chronic Obstructive Pulmonary Disease.

Table 1. Elaboration of the Social Distancing Period Implemented March 12, 2020, in Denmark

Social Distancing Component	Intervention	Period
Distance	1) Keeping 2 m from other people	1) March 12, 2020–May 10, 2020
	2) Keeping 1 m from other people, 2 m from people with symptoms of COVID-19 and people at high risk[a] of complications from COVID-19	2) May 10, 2020–present
Hygiene	Recommendation of frequent handwashing or using hand sanitizer, avoid coughing and sneezing into hands, avoid handshakes, hugs, or kisses as greeting. Mandatory sanitizer facilities in all shops and supermarkets	March 12, 2020–present
Wearing masks	Wearing masks was not recommended in the public space	March 12, 2020–August 22, 2020
Public transport	Call for limited use of public transport, especially in rush hours, and reduced occupancy in public transprot	March 12, 2020–present
Closure of institutions and businesses	1) Closure of indoor public cultural institutions, libraries, and leisure facilities	1) March 13, 2020–May 21, 2020
	2) Closure of all schools and day care centers	2) March 16, 2020–June 24, 2020[b]
	3) Closure of restaurants, cafés, bars, gyms/sport facilities, and malls	3) March 1, 20208–May 18, 2020[c]
	4) Closure of nightclubs	4) March 18, 2020–September 1, 2021
Assembly ban	1) Ban on gatherings of >100 persons	1) March 13, 2020–March 18, 2020
	2) Ban on gatherings of >10 persons	2) March 18, 2020–June 8, 2020
	3) Ban on gatherings of >50 persons	3) June 8, 2020–July 8, 2020
Communication	All above initiatives were communicated through national television, radio broadcasts, advertisements in public spaces, newspapers, web pages, posters, and pamphlets in various languages	March 12, 2020–present

[a] Age >65 years, pregnancy, cardiopulmonary diseases (excluding well-treated hypertension, mild and well-treated asthma), chronic renal disease with reduced renal function, chronic liver disease, type 1 and 2 diabetes, rheumatic and neuromuscular diseases with reduced ability to cough, severe obesity with body mass index >35 (weight (kg)/height (m)^2), hematological diseases with assessed higher risk of complications, children with chronic disease or sequelae of premature birth, and persons with weakened immune system caused by hematological diseases, organ transplantation, immunosuppressive therapy or HIV infection with severe effects on the immune system.

[b] Day care centers, primary school through 5th grade and upper secondary education for graduating students could be opened from April 15, 2020. The entire primary school could open from May 18, 2020; all youth and adult education could reopen from May 27 2020.

[c] Restaurants, cafés, and bars could reopen but had to close at midnight. All shops, malls, and outdoor sports facilities could open from May 8, 2020.

worldwide during winter–spring 2020 to limit the ongoing COVID-19 pandemic. In Denmark, social distancing became required as of midnight on March 12, 2020.

It is well known that s-AECOPD is often triggered by viral or bacterial infections (9). Because viruses other than SARS-CoV-2, as well as bacteria, also depend on well-functioning transmission routes, the incidence of such infections probably will decline during a period of social distancing, and thus incidence of s-AECOPD would decline.

The aim of this semi-experimental study was to determine, in a nationwide population-based cohort, the risk of s-AECOPD in patients with COPD during the social distancing period introduced in Denmark on March 12, 2020, compared with the same period in 2019.

METHODS

The study protocol was posted on the internet (www.coptrin.dk), on May 29, 2020. Analyses began on July 13, 2020, after approval was granted by the Danish Data Protection Agency and receiving access to data from the national health administrative registries.

The social distancing period in Denmark

In the evening of March 11, 2020, a coordinated effort was made by the Danish authorities, politicians, and private organizations to introduce measures to combat COVID-19 in the Danish population (10). Most of these interventions were

Table 2. Characteristics of the Main Study Population as of March 12, 2019, and March 12, 2020, Denmark

Main Cohort Population	Eligible Inhabitants as of March 12, 2019 (*n* = 3,021,189)		Eligible Inhabitants as of March 12, 2020 (*n* = 3,003,468)	
	No.	%	No.	%
Age, years[a]	59 (50–71)		58 (49–71)[a]	
40.00–64.99	1,891,319	62.6	1,842,323	61.3
≥65	1,140,870	37.8	1,161,145	38.7
Male sex	1,477,706	48.9	1,485,613	49.5

[a] Values are expressed as median (interquartile range).

timed to start on March 12, 2020, from midnight; others were to begin on March 13, 2020 (Table 1). In addition, on March 18, 2020, all public places, including schools and day care centers were closed and the assembly ban was lowered to 10 persons. The social distancing period reached its highest level in Denmark to date (Table 1) (11, 12).

Because of the low basic reproduction rate of SARS-CoV-2 infection, the Danish government announced phase 1 of the reopening of Danish society on April 6, 2020 (13), which meant that day care institutions, primary school through 5th grade and upper secondary education for graduating students could be opened from April 15, 2020 (Table 1) (13). On May 8, 2020, phase 2 of the reopening started, during which all stores and malls, among other places, could reopen and outdoor sports could recommence (13) but under certain precautions of continued social distancing. The Danish authorities have introduced laws and, with this legal authority, the police have enforced the interventions, including injunctions and, in certain cases, fines and temporary restraining orders (14). In Denmark, wearing masks in public spaces was not recommended until August 22, 2020 (Table 1).

Study design

According to Danish legislation, informed consent is not required for register-based studies. The study design was an observational, semi-experimental cohort study in which we had 2 cohorts: a main general population cohort for which all incidents of s-AECOPD in Denmark could be registered, thus reducing sample selection bias, and a smaller cohort of patients with COPD, with data on important covariates. We considered the general population cohort for the primary study question, because there are approximately 320,000 patients with COPD in Denmark, half of whom do not know they have COPD (15); therefore, we could register all incidents of s-AECOPD, whether the patients were registered in a COPD database or not.

The main study cohort consisted of all Danish inhabitants found in the Civil Registration System. At date of birth or upon immigration to the country, all Danish citizens receive a unique identification number in the Civil Registration System, which we also used for exact linkage on an individual level between registers, ensuring complete follow-up. Inhabitants younger than 40 years and inhabitants with a diagnosis of COVID-19 were excluded from the study (Figure 1A), with the latter confirmed by the COVID-19 surveillance data from the Danish Microbiology Database and Statens Serum Institute. The main cohort was observed from January 1, 2019, to June 23, 2019, and January 1, 2020, to June 21, 2020 (weeks 1–25 in both years).

A COPD cohort was formed that comprised all Danish outpatients with COPD who were registered in the Danish Register of Chronic Obstructive Pulmonary Disease (DrCOPD), which is a nationwide database containing information on the quality of treatment of patients with COPD in Denmark (16). Since 2008, all Danish hospitals treating patients with COPD have reported to the register, and every patient has been assessed by a respiratory physician who confirmed the COPD diagnosis (*International Classification of Diseases, Tenth Revision*, code J44X). Patients included in the COPD cohort had a respiratory outpatient clinic visit from January 1, 2010 (outpatient clinic visits were registered in the DrCOPD), and follow-up data for 2019 and 2020, if not dead (Figure 1B). Patients younger than 40 years and patients with a diagnosis of COVID-19 were excluded from the study (Figure 1B). The COPD cohort was followed from January 1, 2019, to March 11, 2019; March 12, 2019, to May 20, 2019; January 1, 2020 to March 11, 2020; and March 12 to May 20, 2020.

Exposure variable

The social distancing period in Denmark comprised the interventions described in Table 1. The social distancing period was investigated as the time-varying exposure variable throughout our analyses and was defined as a calendar variable, March 12, 2020, from which the social distancing measures were introduced. In other words, incidents of s-AECOPD on March 12, 2020, and afterward were affected by the exposure variable, whereas incidents of s-AECOPD before March 12, 2020, were not, because these occurred before the social distancing period.

Outcome measures

The outcome of interest was the incidence of s-AECOPD during the observed periods. To identify persons with

Table 3. Characteristics of the Cohort With Chronic Obstructive Pulmonary Disease, as of March 12, 2019, and March 12, 2020, Denmark

COPD Cohort[a]	Patients With COPD Alive on March 12, 2019 (*n* = 16,263)		Patients With COPD Alive on March 12, 2020 (*n* = 14,007)	
	No.	%	No.	%
Age, years[b]	68 (61–74)		67 (60–74)	
Male sex	7,579	46.6	6,479	46.2
FEV_1 % predicted[b]	48 (37–60)		48 (38–60)	
GOLD stage				
4: <30.00	1,766	10.8	1,452	10.4
3: 30.00–49.99	7,283	44.8	6,255	44.7
2: 50.00–79.99	6,442	39.6	5,608	40.0
1: ≥80.00	772	4.7	691	4.9
Body mass index[b,c]	25 (22–29)		25 (22–29)	
<18.50	1,095	6.7	891	6.4
18.50–24.99	5,684	35.0	4,854	34.6
25.00–29.99	5,686	35.0	4,942	35.3
30.00–34.99	2,450	15.1	2,144	15.3
≥ 35.00	1,348	8.3	1,176	8.4
Smoking status				
Active and former ≤6 months	5,821	35.8	5,013	35.8
Former >6 months	10,003	61.5	8,488	60.6
Never	439	2.7	406	2.9
Treatment with LABA/LAMA	13,640	83.9	11,703	83.6
Treatment with ICS	11,614	71.4	9,991	71.3
No. of severe acute exacerbations of COPD 12 months before study period				
0–1	10,164	62.5	8,981	64.1
≥2	6,099	37.5	5,026	35.9
Charlson Comorbidity Index score[d]				
0	8,040	49.4	7,196	51.4
1	3,692	22.7	3,162	22.6
≥2	4,531	27.9	3,649	26.1

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β-adrenergic agonist; LAMA, long-acting muscarinic antagonist.

[a] Specialist-verified COPD.

[b] Values are expressed as median (interquartile range).

[c] Weight (kg)/height $(m)^2$.

[d] Calculated from previous myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, rheumatic disease, peptic ulcer disease, mild liver disease, moderate or severe liver disease, diabetes (with and without complications), hemi- or paraplegia, renal disease, and any malignancy except malignant neoplasm of skin, metastatic cancer. Because all patients had COPD, chronic pulmonary diseases were not included nor was AIDS/HIV infection included, because it is not considered to decrease life expectancy, if treated.

s-AECOPD, a case of s-AECOPD was defined as a primary or secondary diagnosis of s-AECOPD (*International Classification of Diseases, Tenth Revision*, code J40X-44X) in the Danish National Patient Register (DNPR) with the case date specified as the hospital admission date. The DNPR contains information on all admissions to Danish hospitals since 1977 and on hospital outpatient clinic visits since 1995. Each hospital visit is coded with a primary diagnosis by physicians and, if relevant, 1 or more secondary diagnoses (according to the *International Classification of Diseases, Tenth Revision*, from 1994) (17). Furthermore, in the COPD cohort study, admission to an intensive care unit

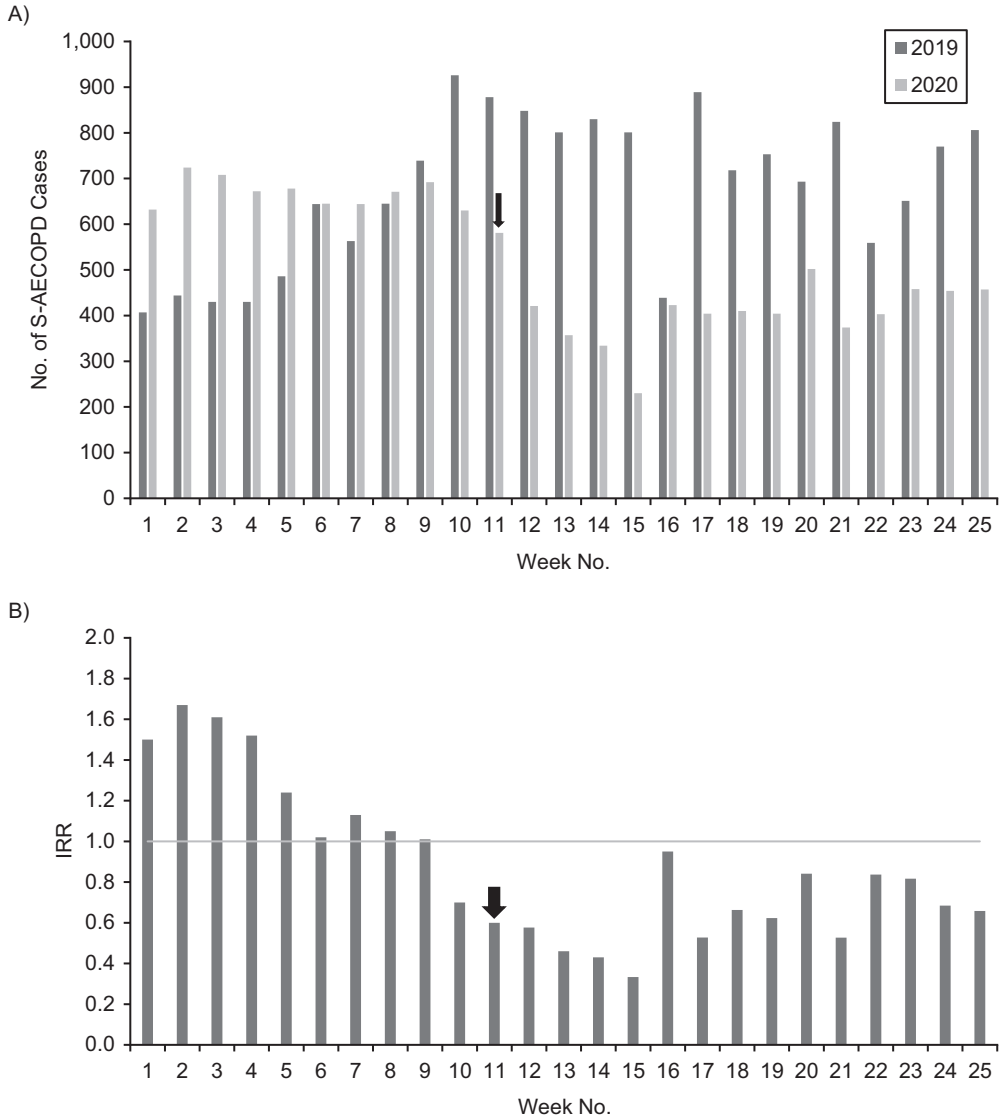

Figure 2. Bar graphs for incidence and incidence rate ratios (IRRs) of severe acute exacerbation of chronic obstructive pulmonary disease (s-AECOPD) in 2019 and 2020 with complete follow-up of 3.0 million inhabitants of Denmark, 2019–2020. The social distancing period started in week 11 in 2020 (black arrows). A) Incidence of s-AECOPD in 2019 and 2020. B) IRR of s-AECOPD in 2020 compared with 2019. Number of incidents of s-AECOPD and IRR per week from calendar week 1 to 25 in 2019 and 2020 in the main study cohort (data on 3.0 million Danish inhabitants from the Danish National Patient Register. IRR was calculated from the incidence rate of s-AECOPD in 2020 divided by the incidence rate of s-AECOPD in 2019; IRR = 1.0 is the reference value.

(ICU) was investigated as a secondary outcome with admission date specified in the DNPR, and all-cause mortality was investigated as the third outcome, assessing the date of death specified in the Civil Registration System.

Statistical analysis

For descriptive statistics, categorical variables were presented as frequencies and proportions, and continuous variables as median values and interquartile ranges (IQRs). In the main cohort, incidence of s-AECOPD was investigated as the sole endpoint, whereas in the COPD cohort, s-AECOPD was investigated as a separate endpoint in a competing risk model with all-cause mortality as the competing event, to avoid attrition bias. Other endpoints were all-cause mortality and ICU admission related to worsening of s-AECOPD; the latter was included in a competing risk model with all-cause mortality as the competing event. The competing risk model used was a Fine-Gray model (18).

The primary analysis was performed with data from the main cohort and used descriptive statistics, counting incidence of s-AECOPD per week from weeks 1–25 in 2019 and 2020 and calculating the incidence rate ratio (IRR) between 2019 and 2020. The social distancing period was from weeks

Table 4. Incidence Rate Ratios of Severe Acute Exacerbation of Chronic Obstructive Pulmonary Disease in 2020 Compared with 2019 in Denmark

Week No.	IRR of s-AECOPD	95% CI
1	1.50	1.32, 1.70
2	1.65	1.47, 1.86
3	1.61	1.43, 1.82
4	1.52	1.35, 1.72
5	1.24	1.10, 1.39
6	1.01	0.91, 1.13
7	1.13	1.01, 1.27
8	1.04	0.93, 1.16
9	1.00	0.90, 1.11
10	0.69	0.62, 0.76
11[a]	0.60	0.54, 0.67
12[a]	0.58	0.52, 0.65
13[a]	0.46	0.41, 0.52
14[a]	0.43	0.38, 0.49
15[a]	0.33	0.29, 0.38
16[a]	0.95	0.83, 1.09
17[a]	0.52	0.46, 0.58
18[a]	0.67	0.59, 0.76
19[a]	0.62	0.55, 0.70
20[a]	0.83	0.74, 0.93
21[a]	0.52	0.46, 0.59
22[a]	0.83	0.73, 0.94
23[a]	0.81	0.72, 0.91
24[a]	0.69	0.61, 0.77
25[a]	0.66	0.59, 0.74

Abbreviations: COPD, chronic obstructive pulmonary disease; IRR, incidence rate ratio; s-AECOPD, severe acute exacerbation of chronic obstructive pulmonary disease.

[a] Postlockdown weeks (weeks 11–25) compared with the pre-lockdown weeks (weeks 1–10); the social distancing period started in week 11 in 2020.

11 to 25 in 2020 and compared with the previous weeks in 2020 and the observed weeks in 2019.

The secondary analysis was conducted in the COPD cohort with an adjusted and extended Cox proportional hazard regression model developed to assess the risk between the social distancing period and s-AECOPD. Here, the social distancing period (as a time-varying covariate) was compared with the period before social distancing in 2020 and also with the observed periods in 2019. The extended Cox model showed proportionality of hazards and linearity of continuous variables, providing evidence the model assumptions were met with no interactions found between the social distancing period and predicted percentage of forced expiratory volume in 1 second ($P = 0.22$) and between social distancing and current smoking ($P = 0.34$). The extended Cox model was adjusted for the following known and suspected confounders assessed at study entry, January 1, 2019, through the DrCOPD, on the basis of previous literature (8, 19–24): age (continuous), sex (male vs. female), severity of airway obstruction based on predicted percentage of forced expiratory volume in 1 second (ordinal: Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 1–4; 1: ≥80%, 2: 50%–79.99%, 3: 30%–49.99%, 4: < 30%), body mass index class (calculated as weight (kg) divided by height squared (m^2); ordinal: 1–5; 1: <18.5, 2: 18.5–24.99, 3: 25–29.99, 4: 30–34.99, 5: ≥35), smoking status (active and former ≤6 months vs. former smoker >6 months vs. never), treatment with a long-acting β-adrenergic agonist or long-acting muscarinic antagonist (yes vs. no), treatment with an inhaled corticosteroid (yes vs. no), number of s-AECOPD episodes in the 12 months prior to study entry (0–1 vs. ≥2), and Charlson Comorbidity Index score (ordinal: 0, 1, ≥2); the latter 2 were assessed via the DNPR. Medication use was defined as a minimum of 2 prescriptions dispensed in the 12 months prior to study entry. Aforementioned covariates are updated at every outpatient clinic visit (outpatients with COPD have 1–4 visits yearly) and if they were not registered at the first outpatient clinic visit, the data from the following visit were imputed. Thus, no patients in the COPD cohort had missing values. Statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Descriptive analyses

In the main cohort, all 3.0 million Danish inhabitants aged ≥40 years (median age, 59 years; 48.9% male inhabitants as of March 12, 2019) were followed in the DNPR for s-AECOPD for a total of 3.0 million person-years (Figure 1A), with characteristics as of March 12, 2019, and March 12, 2020, listed in Table 2.

In the COPD cohort, 16,675 of 131,608 patients with COPD in the DrCOPD registry from January 1, 2010, and with follow-up data in 2019 and 2020 met the inclusion criteria (median age, 68 years; 46.6% male patients as of March 12, 2019) and were followed for a total of 9,940 person-years (Figure 1B). The characteristics for the COPD cohort at study entry were comparable in 2019 and 2020 (Table 3).

Primary analysis

The results of the main outcome analysis are shown in Figure 2A for the incidence of s-AECOPD, in Figure 2B for the IRR of s-AECOPD, and in Table 4 for detailed IRRs of s-AECOPD with 95% confidence intervals (CIs). From the time of lockdown to the end of week 25, there were 6,212 incidents of s-AECOPD, with a mean of 414 incidents per week, compared with 11,260 incidents of s-AECOPD during the same period in 2019, with a mean of 751 incidents per week. This resulted in an absolute reduction of 5,048 incidents of s-AECOPD after the social

Table 5. Extended Cox-Regression Hazard Estimates for s-AECOPD in Chronic Obstructive Pulmonary Disease Cohort[a] (n = 16,675), Comparing Follow-up During Social Distancing in 2020 with Follow-up During Both the Previous Weeks in 2020 and the Observed Period in 2019 When Social Distancing Was Not in Place

Risk of s-AECOPD	COPD Cohort[a] (n = 16,675)			
	Unadjusted sHR	95% CI	Adjusted sHR	95% CI
Social distancing[b]	0.32	0.30, 0.33	0.34	0.33, 0.36
No. of s-AECOPD events during the past 12 months				
0–1	1.00	Referent	1.00	Referent
≥2	1.80	1.73,1.88	1.61	1.54,1.67
GOLD obstruction class increase[c]	1.26	1.22, 1.29	1.17	1.14, 1.21
BMI (per class increase)	0.91	0.90, 0.93	0.96	0.94, 0.98
Treatment with LABA/LAMA	0.68	0.60, 0.75	0.83	0.76, 0.90
Treatment with ICS	0.69	0.62, 0.76	0.87	0.79, 0.98
Smoking status				
Never	1.00	Referent	1.00	Referent
Former (>6 months)	1.12	1.06, 1.19	1.09	1.03, 1.15
Current[d]	1.14	1.07, 1.20	1.10	1.03, 1.16
Charlson Comorbidity Index (per score increase[e])	0.99	0.96, 1.01	1.01	0.99, 1.03
Age (per year)	1.00	1.00, 1.01	1.01	1.00, 1.01
Male sex	0.90	0.87, 0.94	0.92	0.89, 0.96

Abbreviations: BMI, body mass index; CI, confidence interval; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; LABA, long-acting β-adrenergic agonist; LAMA, long-acting muscarinic antagonist; s-AECOPD, severe acute exacerbation of chronic obstructive pulmonary disease; sHR, subdistribution hazard ratio.

[a] Specialist-verified COPD.

[b] Exposure variable (March 12, 2020), in reference to no social distancing (i.e., the periods and s-AECOPD incidents before March 12, 2020).

[c] Increase in predicted percentage of forced expiratory volume in 1 second severity stage (1–4) defined by the GOLD.

[d] Current smoker status includes the categories "active" and "former ≤6 months."

[e] The COPD cohort population could have a Charlson Comorbidity Index score of either 0, 1, or ≥ 2.

distancing period (a 45% relative reduction). The greatest difference in the incidence of s-AECOPD between 2020 and 2019 was in week 15, with 230 incidents of s-AECOPD in 2020 compared with 801 incidents of s-AECOPD in 2019 (IRR = 0.33) (Figure 2). From weeks 10–25, the incidence rate of s-AECOPD was lower in 2020 than in 2019, because the IRR was <1.0 through this period (Figure 2). The exact numbers of s-AECOPD incidents for weeks 1–25 in 2019 and 2020 are reported in Web Tables 1 and 2 (available at https://doi.org/10.1093/aje/kwab292).

Extended Cox analysis in the COPD cohort

The results from the extended Cox analysis conducted in the COPD cohort (n = 16,675) are reported in Table 5 for risk of s-AECOPD, in Table 6 for ICU admission, and in Table 7 for all-cause mortality. Tables 5 and 6 list results from a competing risk model.

There were 3,564 patients with s-AECOPD out of 14,007 patients with COPD (absolute risk: 25.4%) from weeks 11 to 25 in 2020, compared with 6,957 patients with s-AECOPD out of 16,263 patients with COPD (absolute risk = 42.8%) during the same period in 2019. The social distancing period as an exposure variable had a 66% lower incidence of new s-AECOPD incidents (adjusted subdistribution hazard ratio (HR) = 0.34, 95% CI: 0.33, 0.36) compared with when there was no social distancing (i.e., the periods and s-AECOPD incidents before March 12, 2020; hereafter called the "no social distancing period").

In the COPD cohort, there were 332 ICU admissions (out of 14,007 patients; absolute risk = 2.4%) from weeks 11 to 25 in 2020, compared with 494 ICU admissions (out of 16,263 patients; absolute risk = 3.0%) from weeks 11 to 25 in 2019. For ICU admissions, a 36% decreased risk was associated with the social distancing period (adjusted subdistribution HR = 0.64, 95% CI: 0.47, 0.87) compared with the no social distancing period. There were 341 deaths in the COPD cohort (out of 14,007 patients; absolute risk = 2.4%) from weeks 11 to 25 in 2020, compared with 486 deaths (out of 16,263 patients; absolute risk = 3.0%) from weeks 11 to 25 in 2019. For all-cause mortality, a 17% decreased risk was associated with the social distancing period (adjusted HR = 0.83, 95% CI: 0.76, 0.90) compared with the no social distancing period. All analyses were adjusted for the same confounders.

Table 6. Extended Cox Regression Hazard Estimates for Admission to the Intensive Care Unit in Chronic Obstructive Pulmonary Disease Cohort[a] (*n* = 16,675), Comparing Follow-up During Social Distancing in 2020 with Follow-up During Both the Previous Weeks in 2020 and the Observed Period in 2019 When Social Distancing Was Not in Place

Risk of ICU Admission	COPD Cohort[a] (*n* = 16,675)			
	Unadjusted sHR	95% CI	Adjusted sHR	95% CI
Social distancing[b]	0.55	0.40, 0.74	0.64	0.47, 0.87
No. of s-AECOPD events during the last 12 months				
0–1	1.00	Referent	1.00	Referent
≥2	1.42	1.21, 1.68	1.30	1.10, 1.53
GOLD obstruction class increase[c]	1.47	1.31, 1.64	1.46	1.30, 1.64
BMI (per class increase)	1.16	1.08, 1.25	1.22	1.14, 1.32
Treatment with LABA/LAMA	0.97	0.83, 1.26	0.96	0.75, 1.29
Treatment with ICS	1.00	0.79, 1.17	0.92	0.63, 1.25
Smoking status				
Never	1.00	Referent	1.00	Referent
Former(>6 months)	1.18	0.92, 1.53	1.20	0.92, 1.55
Current[d]	1.63	1.27, 2.11	1.58	1.22, 2.04
Charlson Comorbidity Index (per score increase[e])	1.03	0.93, 1.11	1.03	0.98, 1.09
Age (per year)	0.97	0.97, 0.98	0.98	0.97, 0.99
Male sex	0.94	0.80, 1.11	0.86	0.73, 1.01

Abbreviations: BMI, body mass index; CI, confidence interval; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; ICU, intensive care unit; LABA, long-acting β-adrenergic agonist; LAMA, long-acting muscarinic antagonist; s-AECOPD, severe acute exacerbation of chronic obstructive pulmonary disease; sHR, subdistribution hazard ratio.

[a] Specialist-verified COPD.

[b] Exposure variable (March 12, 2020), in reference to no social distancing (i.e., the periods and s-AECOPD-incidents before March 12, 2020).

[c] Increase in predicted percentage of forced expiratory volume in 1 second severity stage (1–4) defined by the GOLD.

[d] Current smoker status includes the categories "active" and "former ≤6 months."

[e] The COPD cohort population could have a Charlson Comorbidity Index score of either 0, 1, or ≥ 2.

DISCUSSION

Using data from a nationwide cohort of 3.0 million Danish inhabitants with a follow-up time of 3.0 million person-years, we found that the social distancing period introduced on March 12, 2020, was associated with a consistent, lower risk of AECOPD requiring hospital admission in the weeks following the intervention, compared with the same periods in 2019. The risk estimates of s-AECOPD associated with the social distancing period were confirmed and were almost in the same range of magnitude in the cohort of outpatients with COPD in 2019 and 2020. Furthermore, the social distancing period was also associated with a decreased risk of admissions to an ICU and decreased all-cause mortality in the COPD cohort.

Tentatively, the lower incidence of s-AECOPD could be caused by a raised threshold for hospital contact during the pandemic rather than a lower incidence of infection; the incidence of other outcomes, such as acute myocardial infarction, heart failure, and atrial fibrillation also decreased (25–27). However, we do not expect this threshold to affect all-cause mortality or ICU admission frequency related to s-AECOPD, and our analyses did show a reduced risk of both these outcomes during the social distancing period. In the COPD cohort, the hazard risk estimates for social distancing were 0.34 for s-AECOPD admissions, 0.64 for ICU admissions (which are less prone to the issue of avoiding medical care), and 0.83 for all-cause mortality (which circumvents this issue). Thereby, it seems reasonable to infer that the 17% lower risk of death represents the most conservative association for ascertaining that the social distancing period did have an influence on clinical outcomes. Furthermore, the biological plausibility that social distancing may causally reduce s-AECOPD is strong because COPD flares are often caused by viral or bacterial infections (9), conditions that social distancing was designed to avoid. The latter possibility supported by several observations that social distancing does reduce the incidence of infections like influenza (7) and COVID-19 (8), and it has been documented that the influenza season in Denmark was abruptly stopped when the social distancing period was introduced (28, 29). Our findings are also consistent with evidence-based guidelines, which recommend influenza and pneumococcal vaccination for patients with COPD to decrease the risk of s-AECOPD (30).

Table 7. Extended Cox Regression Hazard Estimates for All-Cause Mortality in COPD Cohort[a] (*n* = 16,675), Comparing Follow-Up During Social Distancing in 2020 With Follow-Up During Both the Previous Weeks in 2020 and the Observed Period in 2019 when Social Distancing Was Not in Place

Risk of All-Cause Mortality	COPD Cohort[a] (*n* = 16,675)			
	Unadjusted HR	95% CI	Adjusted HR	95% CI
Social distancing[b]	0.82	0.78, 0.87	0.83	0.76, 0.90
No. of s-AECOPD events during the last 12 months				
0–1	1.00	Referent	1.00	Referent
≥2	1.64	1.53, 1.76	1.48	1.38, 1.59
GOLD obstruction class increase[c]	1.18	1.12, 1.24	1.24	1.19, 1.32
BMI (per class increase)	0.90	0.87, 0.94	0.94	0.90, 0.97
Treatment with LABA/LAMA	0.92	0.82, 0.98	0.90	0.77, 1.04
Treatment with ICS	1.04	0.96, 1.12	0.98	0.90, 1.08
Smoking status				
Never	1.00	Referent	1.00	Referent
Former (>6 months)	1.07	0.96, 1.20	1.02	0.92, 1.13
Current[d]	1.25	1.12, 1.39	1.19	1.11, 1.35
Charlson Comorbidity Index (per score increase[e])	1.40	1.35, 1.46	1.31	1.26, 1.37
Age (per year)	1.05	1.05, 1.06	1.05	1.05, 1.06
Male	1.08	1.00, 1.16	1.02	0.95, 1.10

Abbreviations: BMI, body mass index; CI, confidence interval; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; ICS, inhaled corticosteroid; LABA, long-acting β-adrenergic agonist; LAMA, long-acting muscarinic antagonist; s-AECOPD, severe acute exacerbation of chronic obstructive pulmonary disease.

[a] Specialist-verified COPD.

[b] Exposure variable (March 12, 2020), in reference to no social distancing (i.e., the periods and s-AECOPD incidents before March 12, 2020).

[c] Increase in predicted percentage of forced expiratory volume in 1 second severity stage (1–4) defined by the GOLD.

[d] Current smoker status includes the categories "active" and "former ≤6 months."

[e] The COPD cohort population could have a Charlson Comorbidity Index score of either 0, 1, or ≥ 2.

Strengths and limitations

The present study has several strengths compared with other studies regarding social distancing. First, we had a large sample size of approximately 3 million inhabitants of Denmark, which provided us sufficient statistical power. Second, we had data from 2 cohorts with which we could test the same hypothesis; the main population cohort and a well-characterized cohort of patients with COPD; a cohort in which the COPD diagnosis was specialist verified and validated at least once a year (31). In addition, 8 key predictors of outcome were entered for each patient at each clinic visit (e.g., age, sex, level of lung function, smoking status, body mass index, previous s-AECOPD, comorbidities, COPD maintenance treatment), all of which possibly affect the risk of s-AECOPD (8, 19–24). We also virtually compared the same population with each other at different points in time with subtle differences in the actual populations, thus further limiting the impact of potential confounders. Third, our semi-experimental study design enabled us to evaluate the real-world effectiveness of a nationwide intervention, making the study pragmatic. Together with our general population cohort of essentially all Danish residents (excluding those younger than 40 years and/or with a COVID-19 diagnosis), the current study had a high external validity, allowing for generalizability to national populations. Next, a complete follow-up was obtainable on all included persons in the study, because every hospital admission is registered, as is vital status within minutes to few hours upon death. Finally, another strength was the ability to exclude patients with a microbiologically validated COVID-19 diagnosis via real-time nationwide microbiological data.

Although our study has several strengths, some limitations deserve careful consideration. Our data are based on nationwide registers, which do not include information on adherence to the social distancing period (e.g., through questionnaires). This shortcoming could have led to either an overestimation or an underestimation of the effect estimates of social distancing. Another limitation of our data is that the medicine register was not in real time and thus not entirely updated in our observation period. Although only a small fraction of patients with COPD in Denmark change maintenance therapy every month, this could have led to some imprecision. Although we did our best to control for known and suspected confounders and had a semi-experimental study design, we cannot rule out residual confounding due

to unknown confounders and/or model insufficiency. Thus, we cannot infer causation with respect to the observed associations. In addition, our main analysis was based on pre/post observations of the social distancing measures. The ability to strengthen the observation made would be enhanced by observing a predicted increase in s-AECOPD after the relaxation of social distancing measures; however, with the COVID-19 pandemic still underway, this is not yet possible.

Social distancing measures could potentially have a great benefit during nonpandemic times; we demonstrated some of their uses beyond COVID-19 in the present study. We found that 42.8% of our COPD cohort was admitted for s-AECOPD in 2019; this percentage was subsequently reduced to 25.4% in 2020. This high incidence in prepandemic times emphasizes the severity of s-AECOPD as a disease and how important it is to reduce these exacerbations. Patients with COPD could engage in social distancing practices during the winter, when COPD exacerbations (and influenza) are more frequent (32) (e.g., keeping physical distance and minimizing contact with people, frequent handwashing or sanitizer use, and wearing face coverings in public space; although our study did not measure the effect of masks, it could be thought to have an effect on respiratory infections). However, it should be noted that even with the risk reduction from social distancing measures, the incidence of s-AECOPD in 2020 was still high and could be caused by other factors, such as tobacco smoking (33). Furthermore, our results need to be reproduced. Future studies of this intervention should focus on 1) differentiating the effect magnitude of the separate components of the intervention, and 2) finding the negative effects that might also have been a consequence of social distancing in some individuals, such as reduced physical activity and consequent deconditioning, feeling of loneliness, and other psychological consequences.

CONCLUSION

In this nationwide semi-experimental study during a social distancing period, we consistently found a great reduction in risk of severe hospitalization-requiring exacerbation of COPD. Furthermore, when testing the same hypothesis in a well-characterized cohort of outpatients with COPD while adjusting for important confounders, results were confirmed and, additionally, a strong signal was observed in relation to the risk of ICU admission and all-cause death. The impact of this intervention in reducing detrimental outcomes in patients with COPD is promising. However, this needs confirmation, and the most effective elements need to be disentangled from other elements that might be less useful or even harmful.

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The data sets generated and analyzed during this study are not publicly available; they were accessed through a remote connection to servers at the Danish Health Data Authority. Access to the servers requires prior approval from the Danish Data Protection Agency.

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