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Inflammatory bowel disease and risk of severe COVID-19: A nationwide population-based cohort study in Sweden

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Abstract

Background: There are concerns that individuals with chronic immune-mediated diseases are at increased risk of COVID-19 and related severe adverse outcome, including intensive care admission or death. We aimed to explore the absolute and relative risk of severe COVID-19 in inflammatory bowel disease (IBD).

Methods: This population-based cohort study used nationwide registers in Sweden, with 67,292 individuals with a diagnosis of IBD 1969–2017 (Crohn's disease, $n = 21{,}599$; ulcerative colitis: $n = 43{,}622$; IBD-unclassified: $n = 2071$) and alive on 1 February 2020. Patients with IBD were matched to up to five controls from the general population ($n = 297{,}910$). Cox regression estimated hazard ratios (HRs) for (i) hospital admission with laboratory-confirmed COVID-19 as the primary diagnosis, and (ii) severe COVID-19 (composite outcome consisting of (a) COVID-19 intensive care admission, or (b) death from COVID-19 or (c) death within 30 days of COVID-19 hospital admission), were calculated. Analyses were conditioned on age, sex, calendar period, and county and adjusted for other comorbidities.

Results: Between 1 February and 31 July 2020, 179 (0.27%) IBD patients and 500 (0.17%) general population controls were admitted to hospital with COVID-19

(adjusted HR [aHR] = 1.43; 95% CI = 1.19–1.72). The corresponding numbers for severe COVID-19 was 65 (0.10%) and 183 (0.06%; aHR = 1.11; 95% CI = 0.81–1.52). Adjusted HRs were similar in Crohn's disease and ulcerative colitis. In a propensity score-matched model taking comorbidity into account until 2016, the increased risk for COVID-19 hospital admission remained (aHR = 1.32; 1.12–1.56), but there was no increased risk of severe COVID-19 (aHR = 1.12; 0.85–1.47).

Conclusions: While individuals with IBD were more likely to be admitted to hospital for COVID-19 than the general population, the risk of severe COVID-19 was not higher.

KEYWORDS
cohort, COVID-19, IBD, prognosis, SARS-CoV-2

Key Summary

Summarise the established knowledge on this subject

- Individuals with inflammatory bowel disease (IBD) are at increased risk of infections.
- COVID-19 is a pandemic, affecting millions of people.
- COVID-19 can have gastrointestinal manifestations.
- While IBD does not seem to influence the prognosis in COVID-19 positive individuals, data are scarce about the relative and absolute risk of severe COVID-19 in IBD compared with that in the general population.

What are the significant and/or new findings of this study?

- Compared to the general population, individuals with IBD were at increased risk of hospital admission from COVID-19, and this risk increase remained when taking comorbidity into account in a propensity score model.
- However, they were at no increased risk of severe COVID-19 defined as intensive care or death from COVID-19.
- Compared to siblings, individuals with IBD were at no increased risk of hospital admission from COVID-19 or severe COVID-19.
- Even in a country (Sweden) with extensive COVID-19, the absolute risk of severe COVID-19 seems low in IBD. This is comforting to patients and their families.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, relapsing, inflammatory disorder of the gastrointestinal (GI) tract that includes Crohn's diseases (CD) and ulcerative colitis (UC).[1] Its incidence worldwide is increasing.[2] IBD has been linked to an increased risk of death from infections both in adulthood[3–5] (hazard ratio [HR] in Sweden = 2.1; 95% CI = 1.9–2.4)[6] and in childhood (HR = 6.3; 95% CI = 2.1–16.9),[7] potentially due to underlying chronic inflammation, malnutrition and the impact of long-standing immunosuppressive medication exposure.

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[8] During spring, Sweden had no general lockdown and a high mortality rate from COVID-19.[9] While early COVID-19 reports focused on severe respiratory and cardiovascular aspects,[10] recent studies have also reported GI manifestations,[10,11] such as diarrhea (7.7%)[12] and abdominal pain (2.7%).[12]

Recently, Aziz et al.[13] reviewed the literature on IBD and risk of COVID-19. Among 9177 IBD patients in six studies, only 32 patients (0.3%; 95% CI = 0.1%–0.5%) had confirmed COVID-19. The low cumulative incidence of COVID-19 may suggest that IBD patients are not at increased risk of COVID-19, but the reviewed studies did not include general population controls and did not allow for the calculation of relative risks. In a recent Danish study, Attauabi et al.[14] report that IBD patients undergoing testing for COVID-19 were less often positive (2.5%) than in the overall population (3.7% positivity). Derikx et al.[15] reported a lower risk of incident COVID-19, but a higher risk of COVID-19 hospital admission in IBD patients, but their study did not adjust for sex, age or other confounders. In a US multicentre research network study, Singh et al.[16] retrieved data from 31 healthcare organisations. IBD patients with COVID-19 were no more likely to attain the composite outcome of hospital admission or death within 30 days following a diagnosis of COVID-19 compared to non-IBD-patients *with* COVID-19 (relative risk = 0.93; 95% CI = 0.68–1.27). This is consistent

with smaller well-characterised studies from IBD centres.[17] Still, none of these studies calculated relative risks for incident or severe COVID-19 in IBD versus matched general population controls. Additionally, most previous research has largely been limited to IBD referral centres, has not accounted for socioeconomic factors and lacked analyses according to IBD subtypes.

In this nationwide cohort study, we aimed to investigate whether patients with IBD and its subtypes are at increased risk of hospital admission for COVID-19 or severe COVID-19.

METHODS

In Sweden, healthcare is tax-funded and universal. All residents receive a unique personal identity number allowing for register linkages.[18] The current study was restricted to study participants alive on 1 February 2020.

IBD patients

The Swedish Patient Register began in 1964, became nationwide in 1987 and added nonprimary outpatient care in 2001.[19] Diagnoses are coded according to international classification of disease (ICD) codes. For IBD we required ≥1 ICD code for IBD (see Table E1), *and* a GI histopathology record that showed inflammation or was designated as IBD by the pathologist (Table E1).

Histopathology information was retrieved from the ESPRESSO study.[20] This study is based on all computerised GI histopathology records at any of Sweden's 28 pathology departments between 1965 and April 2017. It encompasses 2.1 million individuals. The combination of ICD codes and histopathology to define IBD has been used previously and has a positive predictive value of 95% (95% CI = 89%–99%).[21] Patient Register data on IBD were available up until 31 December 2016, and histopathology data up until 10 April 2017. Date of diagnosis was equal to the second of the two records. According to the first relevant ICD code, IBD patients were furthermore divided into subtypes (CD vs. UC vs. IBD unclassified; Table E1).

Controls

For each individual with IBD, we selected up to five controls from the general population. Controls were matched on age, sex, calendar period and county at time of first GI biopsy. Controls were IBD-free at study entry and were censored if they developed IBD during follow-up).

Siblings

We also examined the risk of COVID-19 in IBD patients compared to unaffected full siblings.

Covariates

In spring 2020, Swedish Ethics Review Boards and government agencies were urged to facilitate COVID-19-related research. A fast track was created that allowed researchers to update existing cohorts with data on deaths and hospital care for COVID-19 (until 31 July 2020) as well as data on death dates (until 31 July 2020). The ESPRESSO cohort was updated accordingly, but the extra ethical permit did not include update of non-COVID-19-related information. For that reason, our data on comorbidity were limited to the original data retrieval for the ESPRESSO cohort (up until 31 December 2016).

We retrieved the following comorbidity data from the Patient Register (hospital-based inpatient and outpatient care): cardiovascular disease including thromboembolic disease, diabetes mellitus, chronic obstructive pulmonary disease, end-stage renal disease, alcohol use disorders including alcohol-related liver disease, obesity/dyslipidaemia, obstructive sleep apnoea, cancer and psychiatric disease (Table E2).

We retrieved data on education as a proxy for socioeconomic status (education, was divided into ≤9, 10–12 and ≥13 years in full time education[22]) as well as country of birth (Nordic vs. not Nordic countries).[23]

Outcomes

In Sweden, it is compulsory to report any positive COVID-19-test to the Swedish Public Health Agency.

We had two main outcomes (i) *hospital admission* with laboratory-confirmed COVID-19 as the primary diagnosis (ICD-10: U07.1), and (ii) *severe COVID-19* (a composite outcome defined as: (a) COVID-19 intensive care admission, or (b) death due to COVID-19 or (c) death within 30 days of diagnosed COVID-19 (U07.1)). Data on COVID-19-specific deaths were obtained through the Cause of Death register[24] (Table E3).

Secondary outcomes were (iii) the above combined (iv) all-cause mortality (COVID-19 or non-COVID-19) or (v) any COVID-19, defined as (a) ICD codes U07.1 and U07.2 (clinically diagnosed COVID-19) in the Patient Register, (b) in the Cause of Death Register or (c) positive record for COVID-19 from the Swedish Public Health Agency or (d) COVID-19 intensive care admission.

In 2020, data on COVID-19 intensive care were prospectively recorded by the Swedish intensive care registry.[25] This register is operative collecting individual patient data from all 83 nonneonatal intensive care units in Sweden. In cooperation with the Public Health Agency of Sweden, mandatory surveillance data of COVID-19 are routinely reported.

Follow-up

Follow-up started on 1 February 2020, and ended with death, record of COVID-19 (according to our outcome definitions) or 31 July 2020.

Statistics

Cox regression conditioned on matching factors (age, sex, county and calendar year) was used to estimate hazard ratios (HRs) for COVID-19. We then adjusted for comorbidities at index date (date of IBD diagnosis, being the second of either an IBD ICD code or the GI histopathology report) and the equivalent date in controls. Our adjusted model also included data on education and country of birth.

We performed subgroup analyses for hospital admission for laboratory verified COVID-19 and for severe COVID-19 according to follow-up (monthly intervals), sex, age at IBD diagnosis (<18, 18–<40, 40–<60, 60+ years), year of diagnosis (1969–1989, 1990–1999, 2000–2009, 2010–2017), IBD subtype (CD, UC, IBD unclassified), country of birth and level of education.

Additional analyses

Rematching using a propensity score model

To test the robustness of our findings, we carried out a second analysis where IBD patients were matched to non-IBD general population controls 1:5 on birth year, sex, county and a nearest neighbour propensity score algorithm allowing a maximum caliper width[26] of 0.2 of the pooled standard deviation of the logit of the propensity score.[27] The logistic regression model included age, sex, education, Nordic country of birth and comorbidities on 31 December 2016. In this analysis, the IBD subtype was based on the last preceding ICD code. Due to lack of controls, the number of IBD-patients in this analysis (n = 67,099) was slightly lower than in the main analysis.

Sibling controls and overall mortality

To minimize the impact of unmeasured confounding we also compared IBD patients to their siblings. Finally, we also examined the risk of overall death in IBD patients admitted to hospital with COVID-19 versus controls admitted with COVID-19; as well as overall death in IBD patients and controls who had at some stage tested positive for COVID-19 (hospital admission not needed). All statistical analyses were performed using SAS (version 9.4) and STATA (version 16.0).

Ethics

This study was approved by the Stockholm Ethics Review Board (no: 2014/1287-31/4, with a COVID-19 specific amendment: 2020-02307). Since this study was based solely on registry data, the review board waived informed consent.[28]

RESULTS

We identified 67,292 Individuals with a diagnosis of IBD between 1969 and 2017 (Crohn's disease, n = 21,599; ulcerative colitis: n = 43,622; IBD-unclassified: n = 2071) and 297,910 matched general population controls (Table 1 and Figure 1). Numbers were similar for the propensity score-matched model (Figure E1). In the sibling analyses we compared 46,607 individuals with IBD and 81,393 siblings.

The median age at IBD diagnosis (second of either ICD diagnosis or histopathology record) was 37.5 years (IQR = 25.7–51.6), with 6569 (9.8%) diagnosed before 18 years of age. Comorbidities were more common in IBD patients both before the index date (date of IBD diagnosis) and before start of follow-up (Table 1).

Characteristics, including IBD subtype, were similar in the rematched propensity-score cohort and in the sibling analyses (Tables E4 and E8).

Main results

During a follow-up of 33,207 person-years, 179 (0.27%) IBD patients were admitted to hospital with COVID-19, compared to 500 (0.17%) general population controls during 147,299 person-years. This corresponded to incidence rates of 5.4 versus 3.4 per 1000 person-years, and an aHR of 1.43 (95% CI = 1.19–1.72; Table 2 and Figure 2).

The aHR was 0.98 (95% CI = 0.54–1.75) for ICU admission, and 1.20 (95% CI = 0.83–1.72) for death.

Sixty-five IBD patients (0.10%) and 183 controls (0.06%) had severe COVID-19 (intensive care admission, death due to COVID-19 or death within 30 days of a COVID-19 diagnosis), yielding incidence rates of 2.0 versus 1.2 per 1000 person-years and an aHR of 1.11 (95% CI = 0.81–1.52; Table 2 and Figure 2).

Subanalyses and secondary outcomes

We found increased risks of COVID-19 hospital admission in patients with IBD throughout follow-up (Table 3); however, statistical power was limited and only risk estimates for follow up periods of 2–<3 months and 5–<6 months were statistically significant. HRs for COVID-19 hospital admission did not differ by sex, age at IBD diagnosis, calendar year of diagnosis, country of birth or level of education (all p interaction > 0.05). The aHR for COVID-19 hospital admission was 1.55 (95% CI = 1.11–2.17) in CD, and 1.40 (1.11–1.77) in UC. For severe COVID-19 the aHRs were 1.44 (95% CI = 0.69–3.00) and 1.10 (0.75–1.60) respectively (Table 4). IBD patients were at increased risk of overall death during the study period (aHR = 1.19, 95% CI = 1.07–1.33).

TABLE 1 Baseline characteristics of study cohort

Characteristic	IBD (*n* = 67,292)	Matched comparators (*n* = 297,910)
Females, no. (%)	32,971 (49.0%)	147,807 (49.6%)
Males, no (%)	34,321 (51.0%)	150,103 (50.4%)
Age at index date		
Mean (*SD*)	39.1 (16.8)	38.0 (16.2)
Median (IQR)	37.5 (25.7–51.6)	36.4 (25.1–49.9)
Categories, no. (%)		
<18 years	6569 (9.8%)	30,891 (10.4%)
18–<40 years	30,299 (45.0%)	139,734 (46.9%)
40–<60 years	21,515 (32.0%)	94,338 (31.7%)
≥60 years	8909 (13.2%)	32,947 (11.1%)
Age at start of follow-up		
Mean (*SD*)	53.9 (17.4)	52.4 (16.8)
Median (IQR)	54.2 (40.2–67.9)	52.8 (39.2–65.9)
Range, min-max	4.5–99.8	4.5–100.0
Categories, no. (%)		
<18 Years	608 (0.9%)	2984 (1.0%)
18–<40 Years	16 023 (23.8%)	75,657 (25.4%)
40–<60 Years	24,345 (36.2%)	112,864 (37.9%)
≥60 Years	26,316 (39.1%)	106,405 (35.7%)
Country of birth, no (%)		
Nordic country	61,761 (91.8%)	263,829 (88.6%)
Other	5527 (8.2%)	34,067 (11.4%)
Missing	4 (0.0%)	14 (0.0%)
Level of education, no (%)[a]		
≤9 Years	14,528 (21.6%)	61,575 (20.7%)
10–12 Years	31,596 (47.0%)	136,338 (45.8%)
>12 Years	20,313 (30.2%)	94,556 (31.7%)
Missing	855 (1.3%)	5441 (1.8%)
Index year		
1969–1989	3112 (4.6%)	12,488 (4.2%)
1990–1999	12,037 (17.9%)	50,685 (17.0%)
2000–2009	29,228 (43.4%)	128,191 (43.0%)
2010–2017	22,915 (34.1%)	106,546 (35.8%)
IBD disease		
CD	21,599 (32.1%)	
UC	43,622 (64.8%)	
IBD-U	2071 (3.1%)	
Disease history ever before index date, no. (%)		
Any cardiovascular disease	5933 (8.8%)	14 515 (4.9%)
Diabetes	1818 (2.7%)	5165 (1.7%)

(Continues)

TABLE 1 (Continued)

Characteristic	IBD (*n* = 67,292)	Matched comparators (*n* = 297,910)
COPD[b]	659 (1.0%)	1287 (0.4%)
End-stage renal disease	158 (0.2%)	214 (0.1%)
Alcohol liver disease and alcohol use disorder	1407 (2.1%)	5672 (1.9%)
Obesity/dyslipidaemia	1856 (2.8%)	6152 (2.1%)
Obstructive sleep apnoea	687 (1.0%)	2131 (0.7%)
Cancer	2049 (3.0%)	5547 (1.9%)
Psychiatric disease	5672 (8.4%)	20,439 (6.9%)
Disease history ever before start of follow-up, no. (%)		
Any cardiovascular disease	15,575 (23.1%)	44,042 (14.8%)
Diabetes	4597 (6.8%)	13,094 (4.4%)
COPD[b]	1892 (2.8%)	4082 (1.4%)
End-stage renal disease	489 (0.7%)	623 (0.2%)
Alcohol liver disease and alcohol use disorder	2656 (3.9%)	11,072 (3.7%)
Obesity/dyslipidaemia	5412 (8.0%)	20,027 (6.7%)
Obstructive sleep apnoea	2208 (3.3%)	7590 (2.5%)
Cancer	5385 (8.0%)	15,901 (5.3%)
Psychiatric disease	12,279 (18.2%)	43,141 (14.5%)
Follow-up to hospital admission, months		
Mean (*SD*)	5.9 (0.3)	5.9 (0.3)
Median (IQR)	6.0 (6.0–6.0)	6.0 (6.0–6.0)
Range, min-max	0.0–6.0	0.0–6.0

[a]Using highest level of education in parents when education data was missing.

[b]COPD, Chronic obstructive pulmonary disease.

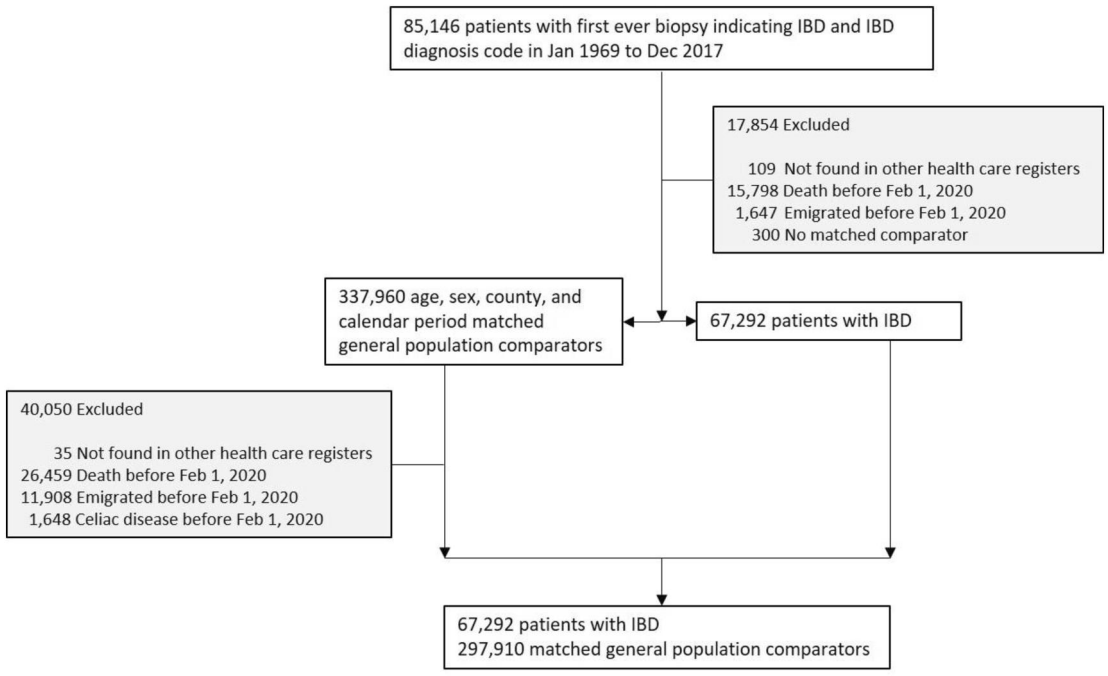


FIGURE 1 Flow chart of identified patients and their matched comparators

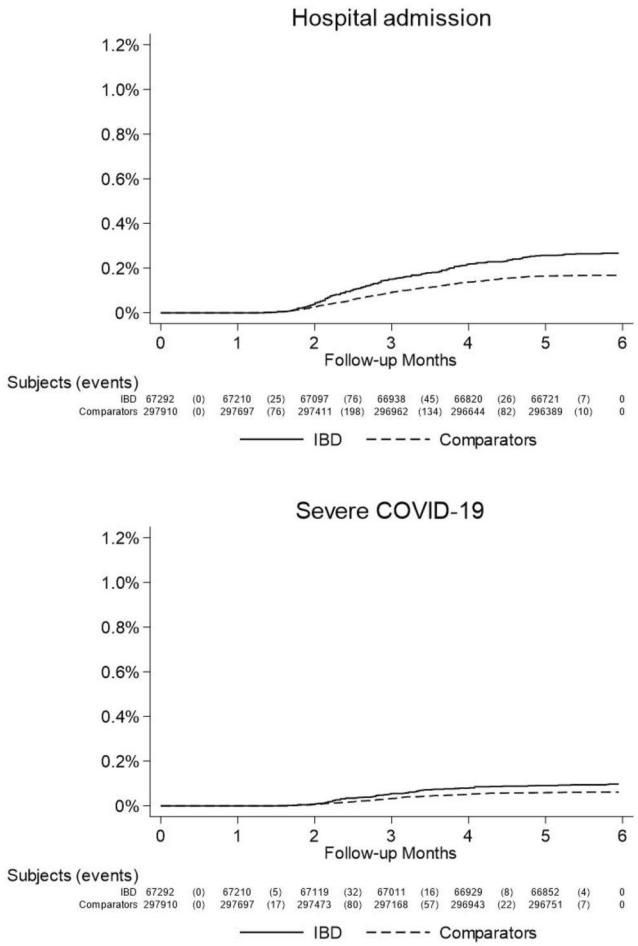
TABLE 2 Risk of COVID-19 in patients with IBD and matched general population comparators from 1 February to 31 July 2020 (*n* IBD/*n* comparators = 67,292/297,910)

	N events (%)		Time at risk (years)		Incidence rate (95% CI) per 1000 PY			
Outcome	**IBD**	**Comparators**	**IBD**	**Comparators**	**IBD**	**Comparators**	**HR[a] (95% CI)**	**HR[b] (95% CI)**
Main outcomes								
Hospital admission	179 (0.27%)	500 (0.17%)	33,207	147,299	5.4 (4.6–6.2)	3.4 (3.1–3.7)	1.45 (1.22–1.72)	1.43 (1.19–1.72)
Severe COVID-19[c]	65 (0.10%)	183 (0.06%)	33,239	147,389	2.0 (1.5–2.4)	1.2 (1.1–1.4)	1.24 (0.92–1.66)	1.11 (0.81–1.52)
Intensive care admission	18 (0.03%)	80 (0.03%)	33,239	147,389	0.5 (0.3–0.8)	0.5 (0.4–0.7)	0.96 (0.57–1.60)	0.98 (0.54–1.75)
Death due to COVID-19	53 (0.08%)	122 (0.04%)	33,242	147,405	1.6 (1.2–2.0)	0.8 (0.7–1.0)	1.40 (1.00–1.96)	1.20 (0.83–1.72)
Secondary outcomes								
Main outcomes combined	202 (0.30%)	558 (0.19%)	33,206	147,297	6.1 (5.2–6.9)	3.8 (3.5–4.1)	1.42 (1.21–1.68)	1.38 (1.16-1.64)
All-cause mortality	486 (0.72%)	1265 (0.42%)	33,242	147,405	14.6 (13.3–15.9)	8.6 (8.1–9.1)	1.31 (1.17–1.45)	1.19 (1.07–1.33)
Any COVID-19	811 (1.21%)	2890 (0.97%)	33,093	146,880	24.5 (22.8–26.2)	19.7 (19.0–20.4)	1.23 (1.13–1.33)	1.21 (1.12–1.31)

[a]Conditioned on matching set (age, sex, county and calendar period).

[b]Conditioned on matching set and further adjusted for education, Nordic country of birth and medical comorbidities at index date (cardiovascular disease, diabetes, COPD, end-stage renal disease, alcohol liver disease/alcohol use disorder, obesity/dyslipidaemia, obstructive sleep apnoea, cancer, psychiatric disease).

[c]Intensive care admission and death can occur in the same individual. Hence, the numbers of ICU admissions and deaths are not equal to the number of severe COVID-19.



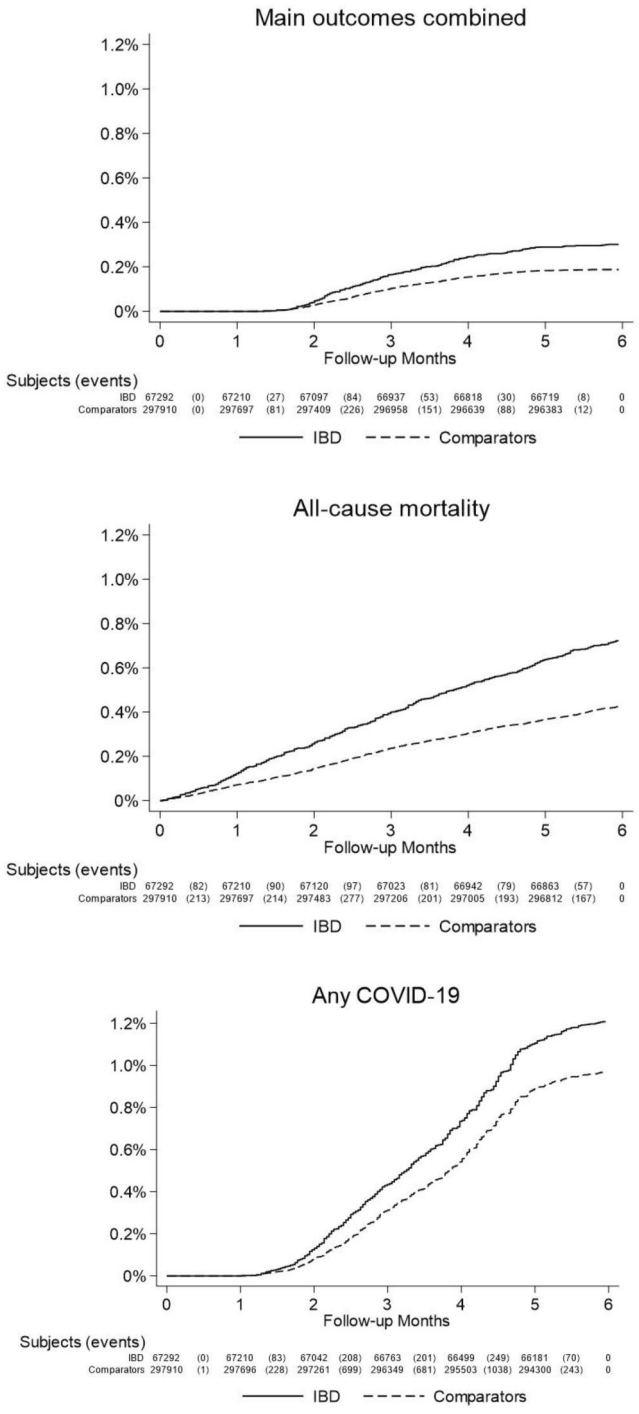


FIGURE 2 a) Kaplan–Meier failure curves of time to main outcomes of coronavirus disease-2019 (COVID-19) infection in patients with IBD and in matched comparators from 1 February to 31 July 2020. (b)Kaplan–Meier failure curves of time to secondary outcomes of COVID-19 infection in patients with inflammatory bowel disease and in matched comparators from 1 February 1 to 31 July 2020

FIGURE 2 (Continued)

Risk of incident COVID-19

IBD patients were also at a 21% increased risk of any COVID-19 (Table 2). In total, 811 (1.21%) IBD patients and 2890 (0.97%) controls had a record of any COVID-19 (Table 2).

Additional analyses

In a propensity score-matched model taking comorbidity until 2016 into account, the increased risk for COVID-19 hospital admission persisted (aHR = 1.32; 1.12–1.56), but there was no increased risk of severe COVID-19 (aHR = 1.12; 0.85–1.47) (Tables E5–E7 and Figure E2).

Sibling analyses yielded similar results (aHR for COVID-19 hospital admission was 1.25; and 1.18 for severe COVID-19), although none of these risk estimates attained statistical significance (Table 5 and Figure E3).

Finally, restricting our sample to IBD patients and controls who were COVID-19 positive or admitted to hospital for COVID-19, IBD status was not associated with subsequent death (Tables E9 and E10). Out of 179 IBD patients admitted to hospital with COVID-19, 32 (17.9%) died during follow-up. This compared with 72 (14.4%) deaths

TABLE 3 Risk of hospital admission for COVID-19 overall and by subgroups in patients with IBD and matched general population comparators from 1 February to 31 July 2020.

	N (%)		*N* events (%)		Incidence rate (95% CI) per 1000 PY			
Group	**IBD**	**Comparators**	**IBD**	**Comparators**	**IBD**	**Comparators**	**HR[a] (95% CI)**	**HR[b] (95% CI)**
Overall	67,292 (100%)	297,910 (100%)	179 (0.27%)	500 (0.17%)	5.4 (4.6–6.2)	3.4 (3.1–3.7)	1.45 (1.22–1.72)	1.43 (1.19–1.72)
Follow-up								
0–<1 m	67,292 (100%)	297,910 (100%)	0	0	0	0	–	–
1–<2 m	67,210 (99.9%)	297,697 (99.9%)	25 (0.04%)	76 (0.03%)	4.5 (2.7–6.2)	3.1 (2.4–3.8)	1.37 (0.87–2.16)	1.53 (0.93–2.52)
2–<3 m	67,097 (99.7%)	297,411 (99.8%)	76 (0.11%)	198 (0.07%)	13.6 (10.5–16.7)	8.0 (6.9–9.1)	1.61 (1.23–2.11)	1.56 (1.17–2.09)
3–<4 m	66,938 (99.5%)	296,962 (99.7%)	45 (0.07%)	134 (0.05%)	8.1 (5.7–10.4)	5.4 (4.5–6.3)	1.29 (0.91–1.81)	1.28 (0.88–1.85)
4–<5 m	66,820 (99.3%)	296,644 (99.6%)	26 (0.04%)	82 (0.03%)	4.7 (2.9–6.5)	3.3 (2.6–4.0)	1.23 (0.79–1.93)	1.26 (0.78–2.04)
5–<6 m	66,721 (99.2%)	296,389 (99.5%)	7 (0.01%)	10 (0.00%)	1.3 (0.3–2.3)	0.4 (0.2–0.7)	2.95 (1.12–7.78)	4.48 (1.09–18.35)
Sex								
Females	32,971 (49.0%)	147,807 (49.6%)	80 (0.24%)	208 (0.14%)	4.9 (3.8–6.0)	2.8 (2.5–3.2)	1.59 (1.22–2.06)	1.59 (1.20–2.11)
Males	34,321 (51.0%)	150,103 (50.4%)	99 (0.29%)	292 (0.19%)	5.8 (4.7–7.0)	3.9 (3.5–4.4)	1.35 (1.07–1.70)	1.34 (1.05–1.72)
Age at index date								
<18 years	6569 (9.8%)	30,891 (10.4%)	6 (0.09%)	9 (0.03%)	1.8 (0.4–3.3)	0.6 (0.2–1.0)	2.97 (1.05–8.38)	2.93 (0.96–8.92)
18–<40 years	30,299 (45.0%)	139,734 (46.9%)	41 (0.14%)	134 (0.10%)	2.7 (1.9–3.6)	1.9 (1.6–2.3)	1.39 (0.98–1.97)	1.52 (1.05–2.21)
40–<60 years	21,515 (32.0%)	94,338 (31.7%)	75 (0.35%)	219 (0.23%)	7.1 (5.5–8.7)	4.7 (4.1–5.3)	1.44 (1.10–1.88)	1.49 (1.12–1.98)
≥60 years	8909 (13.2%)	32,947 (11.1%)	57 (0.64%)	138 (0.42%)	13.1 (9.7–16.6)	8.5 (7.1–10.0)	1.40 (1.02–1.93)	1.23 (0.87–1.72)
Index year								
1969–1989	3112 (4.6%)	12,488 (4.2%)	11 (0.35%)	28 (0.22%)	7.2 (2.9–11.4)	4.5 (2.9–6.2)	1.51 (0.74–3.07)	1.52 (0.71–3.28)
1990–1999	12,037 (17.9%)	50,685 (17.0%)	30 (0.25%)	90 (0.18%)	5.1 (3.2–6.9)	3.6 (2.9–4.3)	1.25 (0.82–1.89)	1.23 (0.78–1.93)
2000–2009	29,228 (43.4%)	128,191 (43.0%)	80 (0.27%)	223 (0.17%)	5.5 (4.3–6.8)	3.5 (3.1–4.0)	1.45 (1.12–1.88)	1.47 (1.12–1.95)
2010–2017	22,915 (34.1%)	106,546 (35.8%)	58 (0.25%)	159 (0.15%)	5.1 (3.8–6.4)	3.0 (2.5–3.5)	1.55 (1.14–2.11)	1.40 (1.00–1.96)
Age at start of follow-up								
<18 years	608 (0.9%)	2984 (1.0%)	1 (0.16%)	0	3.3 (0.0–9.8)	0	–	–
18–<40 years	16,023 (23.8%)	75,657 (25.4%)	11 (0.07%)	27 (0.04%)	1.4 (0.6–2.2)	0.7 (0.4–1.0)	1.87 (0.93–3.77)	2.11 (0.93–4.80)
40–<60 years	24,345 (36.2%)	112,864 (37.9%)	46 (0.19%)	157 (0.14%)	3.8 (2.7–4.9)	2.8 (2.4–3.2)	1.37 (0.98–1.90)	1.49 (1.04–2.14)
≥60 years	26,316 (39.1%)	106,405 (35.7%)	121 (0.46%)	316 (0.30%)	9.4 (7.7–11.0)	6.0 (5.4–6.7)	1.44 (1.16–1.78)	1.36 (1.09–1.71)

(Continues)

TABLE 3 (Continued)

	N (%)		*N* events (%)		Incidence rate (95% CI) per 1000 PY			
Group	**IBD**	**Comparators**	**IBD**	**Comparators**	**IBD**	**Comparators**	**HR[a] (95% CI)**	**HR[b] (95% CI)**
IBD disease								
CD	21,599 (32.1%)	96,287 (32.3%)	60 (0.28%)	146 (0.15%)	5.6 (4.2–7.1)	3.1 (2.6–3.6)	1.66 (1.22–2.25)	1.55 (1.11–2.17)
UC	43,622 (64.8%)	192,202 (64.5%)	112 (0.26%)	335 (0.17%)	5.2 (4.2–6.2)	3.5 (3.1–3.9)	1.36 (1.10–1.69)	1.40 (1.11–1.77)
IBD–U	2071 (3.1%)	9421 (3.2%)	7 (0.34%)	19 (0.20%)	6.9 (1.8–11.9)	4.1 (2.2–5.9)	1.33 (0.55–3.21)	0.86 (0.25–2.92)
Country of birth								
Nordic	61,761 (91.8%)	263,829 (88.6%)	150 (0.24%)	344 (0.13%)	4.9 (4.1–5.7)	2.6 (2.4–2.9)	1.69 (1.39–2.07)	1.52 (1.23–1.87)
Other	5527 (8.2%)	34,067 (11.4%)	29 (0.52%)	156 (0.46%)	10.6 (6.8–14.5)	9.3 (7.8–10.7)	1.35 (0.59–3.13)	1.54 (0.60–3.96)
Level of education								
≤9 years	14,528 (21.6%)	61,575 (20.7%)	48 (0.33%)	139 (0.23%)	6.7 (4.8–8.6)	4.6 (3.8–5.3)	1.39 (0.84–2.30)	1.31 (0.75–2.27)
10–12 years	31,596 (47.0%)	136,338 (45.8%)	79 (0.25%)	208 (0.15%)	5.1 (3.9–6.2)	3.1 (2.7–3.5)	1.64 (1.20–2.25)	1.52 (1.08–2.15)
>12 years	20,313 (30.2%)	94,556 (31.7%)	43 (0.21%)	127 (0.13%)	4.3 (3.0–5.6)	2.7 (2.2–3.2)	1.94 (1.22–3.09)	2.20 (1.31–3.68)

[a]Conditioned on matching set (age, sex, county and calendar period).

[b]Conditioned on matching set and further adjusted for education, Nordic country of birth and medical comorbidities at index date (cardiovascular disease, diabetes, COPD, end-stage renal disease, alcohol liver disease/alcohol use disorder, obesity/dyslipidemia, obstructive sleep apnea, cancer, psychiatric disease).

TABLE 4 Risk of severe COVID-19 overall and by subgroups in patients with IBD and matched general population comparators from 1 February to 31 July 2020

	N (%)		*N* events (%)		Incidence Rate (95% CI) per 1000 PY			
Group	**IBD**	**Comparators**	**IBD**	**Comparators**	**IBD**	**Comparators**	**HR[a] (95%CI)**	**HR[b] (95%CI)**
Overall	67,292 (100%)	297,910 (100%)	65 (0.10%)	183 (0.06%)	2.0 (1.5–2.4)	1.2 (1.1–1.4)	1.24 (0.92–1.66)	1.11 (0.81–1.52)
Follow-up								
0–<1 m	67,292 (100%)	297,910 (100%)	0	0	0	0	–	–
1–<2 m	67,210 (99.9%)	297,697 (99.9%)	5 (0.01%)	17 (0.01%)	0.9 (0.1–1.7)	0.7 (0.4–1.0)	1.05 (0.38–2.90)	1.59 (0.42–5.97)
2–<3 m	67,119 (99.7%)	297,473 (99.9%)	32 (0.05%)	80 (0.03%)	5.7 (3.7–7.7)	3.2 (2.5–3.9)	1.58 (1.04–2.41)	1.49 (0.95–2.34)
3–<4 m	67,011 (99.6%)	297,168 (99.8%)	16 (0.02%)	57 (0.02%)	2.9 (1.5–4.3)	2.3 (1.7–2.9)	0.89 (0.50–1.59)	0.87 (0.44–1.69)
4–<5 m	66,929,(99.5%)	296,943 (99.7%)	8,(0.01%)	22 (0.01%)	1.4 (0.4–2.4)	0.9 (0.5–1.3)	0.97 (0.42–2.24)	0.33 (0.08–1.36)
5–<6 m	66,852 (99.3%)	296,751 (99.6%)	4 (0.01%)	7 (0.00%)	0.8 (0.0–1.5)	0.3 (0.1–0.5)	2.07 (0.56–7.63)	2.58 (0.25–27.02)
Sex								
Females	32,971 (49.0%)	147,807 (49.6%)	25 (0.08%)	67 (0.05%)	1.5 (0.9–2.1)	0.9 (0.7–1.1)	1.29 (0.80–2.08)	1.14 (0.67–1.97)
Males	34,321 (51.0%)	150,103 (50.4%)	40 (0.12%)	116 (0.08%)	2.4 (1.6–3.1)	1.6 (1.3–1.8)	1.21 (0.83–1.75)	1.12 (0.75–1.67)
Age at index date								
<18 years	6569 (9.8%)	30,891 (10.4%)	0	0	0	0	–	–
18–<40 years	30,299 (45.0%)	139,734 (46.9%)	5 (0.02%)	31 (0.02%)	0.3 (0.0–0.6)	0.4 (0.3–0.6)	0.74 (0.29–1.92)	0.90 (0.32–2.50)
40–<60 years	21,515 (32.0%)	94,338 (31.7%)	22 (0.10%)	71 (0.08%)	2.1 (1.2–2.9)	1.5 (1.2–1.9)	1.20 (0.74–1.94)	1.06 (0.62–1.82)
≥60 years	8909 (13.2%)	32,947 (11.1%)	38 (0.43%)	81 (0.25%)	8.7 (6.0–11.5)	5.0 (3.9–6.1)	1.42 (0.94–2.13)	1.16 (0.74–1.81)
Index year								
1969–1989	3112 (4.6%)	12,488 (4.2%)	2 (0.06%)	9 (0.07%)	1.3 (0.0–3.1)	1.5 (0.5–2.4)	0.60 (0.13–2.88)	0.23 (0.03–1.90)
1990–1999	12,037 (17.9%)	50,685 (17.0%)	11 (0.09%)	33 (0.07%)	1.9 (0.8–2.9)	1.3 (0.9–1.8)	1.08 (0.53–-2.19)	0.93 (0.41–2.12)
2000–2009	29,228 (43.4%)	128,191 (43.0%)	31 (0.11%)	89 (0.07%)	2.1 (1.4–2.9)	1.4 (1.1–1.7)	1.20 (0.78–1.83)	1.20 (0.75–1.90)
2010–2017	22,915 (34.1%)	106,546 (35.8%)	21 (0.09%)	52 (0.05%)	1.9 (1.1–2.6)	1.0 (0.7–1.3)	1.57 (0.93–2.64)	1.08 (0.58–2.03)
Age at start of follow-up								
<18 years	608 (0.9%)	2984 (1.0%)	0	0	0	0	–	–
18–<40 years	16,023 (23.8%)	75,657 (25.4%)	(0.00%)	5 (0.01%)	0.0 (0.0–0.0)	0.1 (0.0–0.3)	0.00 (0.00–.)	0.00 (0.00–.)
40–<60 years	24,345 (36.2%)	112,864 (37.9%)	4 (0.02%)	33 (0.03%)	0.3 (0.0–0.7)	0.6 (0.4–0.8)	0.55 (0.19–1.55)	0.58 (0.18–1.85)
≥60 years	26,316 (39.1%)	106,405 (35.7%)	61 (0.23%)	145 (0.14%)	4.7 (3.5–5.9)	2.8 (2.3–3.2)	1.41 (1.04–1.93)	1.25 (0.90–1.75)

(Continues)

TABLE 4 (Continued)

Group	*N* (%)		*N* events (%)		Incidence Rate (95% CI) per 1000 PY		HR[a] (95%CI)	HR[b] (95%CI)
	IBD	Comparators	IBD	Comparators	IBD	Comparators		
IBD disease								
CD	21,599 (32.1%)	96,287 (32.3%)	20 (0.09%)	38 (0.04%)	1.9 (1.1–2.7)	0.8 (0.5–1.1)	1.79 (1.02–3.14)	1.44 (0.69–3.00)
UC	43,622 (64.8%)	192,202 (64.5%)	42 (0.10%)	134 (0.07%)	1.9 (1.4–2.5)	1.4 (1.2–1.6)	1.08 (0.75–1.54)	1.10 (0.75–1.60)
IBD–U	2071 (3.1%)	9421 (3.2%)	3 (0.14%)	11 (0.12%)	2.9 (0.0–6.3)	2.4 (1.0–3.8)	1.28 (0.34–4.77)	0.88 (0.14–5.55)
Country of birth								
Nordic	61,761 (91.8%)	263,829 (88.6%)	56 (0.09%)	144 (0.05%)	1.8 (1.4–2.3)	1.1 (0.9–1.3)	1.32 (0.95–1.84)	1.16 (0.81–1.65)
Other	5527 (8.2%)	34,067 (11.4%)	9 (0.16%)	39 (0.11%)	3.3 (1.1–5.4)	2.3 (1.6–3.0)	1.67 (0.22–12.82)	1.14 (0.04–34.99)
Level of education								
≤9 years	14,528 (21.6%)	61,575 (20.7%)	26 (0.18%)	58 (0.09%)	3.6 (2.2–5.0)	1.9 (1.4–2.4)	1.11 (0.48–2.59)	0.85 (0.32–2.24)
10–12 years	31,596 (47.0%)	136,338 (45.8%)	24 (0.08%)	74 (0.05%)	1.5 (0.9–2.2)	1.1 (0.8–1.3)	1.32 (0.74–2.35)	1.29 (0.69–2.43)
>12 years	20,313 (30.2%)	94,556 (31.7%)	13 (0.06%)	41 (0.04%)	1.3 (0.6–2.0)	0.9 (0.6–1.1)	1.98 (0.85–4.58)	2.59 (0.88–7.64)

[a]Conditioned on matching set (age, sex, county and calendar period).

[b]Conditioned on matching set and further adjusted for education, Nordic country of birth and medical comorbidities at index date (cardiovascular disease, diabetes, COPD, end-stage renal disease, alcohol liver disease/alcohol use disorder, obesity/dyslipidemia, obstructive sleep apnea, cancer, psychiatric disease).

TABLE 5 Risk of COVID-19 in patients with IBD and siblings from 1 February to 31 July 2020 (*n* IBD/*n* siblings = 46,607/81,393)

	N events (%)		Time at risk (years)		Incidence rate (95% CI) per 1000 PY			
Outcome	IBD	Siblings	IBD	Siblings	IBD	Siblings	HR[a] (95% CI)	HR[b] (95% CI)
Main outcomes								
Hospital admission	94 (0.20%)	127 (0.16%)	23,032	40,245	4.1 (3.3–4.9)	3.2 (2.6–3.7)	1.31 (1.00–1.73)	1.25 (0.93–1.69)
Severe COVID-19	25 (0.05%)	43 (0.05%)	23,050	40,269	1.1 (0.7–1.5)	1.1 (0.7–1.4)	1.03 (0.62–1.71)	1.18 (0.64–2.19)
Secondary outcomes								
Main outcomes combined	104 (0.22%)	141 (0.17%)	23,032	40,245	4.5 (3.6–5.4)	3.5 (2.9–4.1)	1.31 (1.00–1.70)	1.24 (0.93–1.65)
All-cause mortality	228 (0.49%)	322 (0.40%)	23,052	40,273	9.9 (8.6–11.2)	8.0 (7.1–8.9)	1.35 (1.13–1.62)	1.30 (1.06–1.59)
Any COVID-19	507 (1.09%)	741 (0.91%)	22,958	40,137	22.1 (20.2–24.0)	18.5 (17.1–19.8)	1.18 (1.05–1.32)	1.13 (1.00–1.28)

[a]Conditioned on matching set (family).

[b]Conditioned on matching set and further adjusted for age, sex, education, Nordic country of birth and medical comorbidities at index date (cardiovascular disease, diabetes, COPD, end-stage renal disease, alcohol liver disease/alcohol use disorder, obesity/dyslipidemia, obstructive sleep apnea, cancer, psychiatric disease).

among controls hospitalised with COVID-19. Adjusting for confounders, this resulted in an aHR of 1.08 (95% CI = 0.70–1.68).

DISCUSSION

In this nationwide population-based cohort study, we observed an increased risk of hospital-admission for COVID-19 but no significant association with severe COVID-19 among more than 67,000 individuals with IBD. Results were similar for CD and UC, and were robust in sensitivity analyses after propensity score-matching and when comparing IBD patients to their siblings.

Research on IBD and COVID-19 evolved from how to manage patients during the pandemic,[29–32] followed by patient series from larger centres with COVID-19,[17,33,34] and research on risk factors for COVID-19 or severe COVID-19 in the IBD patient population.[35,36] A recent Danish study by Attauabi et al.[14] examined three cohorts with regards to IBD and COVID-19; (i) patients with both IBD and COVID-19 (n = 76); (ii) individuals with IBD who had been screened for COVID-19 in parts of Denmark (UC: n = 11,458, and CD: n = 6878); and (iii) IBD patients who responded to a survey on their mental health during the pandemic (n = 2000). While the second cohort is similar to ours, the authors focused on the proportion of tested cases who were positive for SARS-COV-2. They did not calculate absolute and relative risks of any or severe COVID-19 in IBD compared to the general population.

In the present study, and differing from earlier research, we neither restricted our population exclusively to IBD patients nor to patients who are COVID-19 positive. Rather, we took advantage of the Swedish national healthcare registers and compared IBD patients to general population controls.

We found an increased risk of hospital admission for COVID-19, one of our two main outcomes. Despite this finding, the magnitude of the risk was small, in both absolute and relative terms. During the study period, one in 185 IBD patients was admitted to hospital for COVID-19 compared with one in 295 controls (or one in 249 co-morbidity-matched controls). These incidence rates corresponded to a 43% increased risk of hospital admission for COVID-19, but importantly, this did not translate into an increased risk of *severe* COVID-19, defined as requirement for intensive care or death. Neither did we see an increased risk of death among IBD patients who were hospitalised with COVID-19.

There could be several explanations for our findings. Viral SARS-COV-2 RNA has been detected in faecal samples,[37,38] and the receptor for viral cell entry, *angiotensin-converting enzyme 2*,[39] is expressed in GI epithelial cells.[40] This suggest that faecal-oral transmission may represent a possible transmission route, and we cannot rule out that IBD is associated with a truly increased risk of SARS-CoV-2 acquisition or COVID-19. Another reason for the association with hospital admission could be a tendency among physicians to test IBD patients for COVID-19 more often than the general population (as seen in the study by Attauabi et al.[14]), and a tendency to admit IBD patients with COVID-19 out of cautiousness.

Although, our study does not exclude the possibility of an increased risk of severe COVID-19 (the 95% upper CI was 1.52), the adjusted HR of 1.11 may assist in providing reassurance to IBD patients and their families that IBD does not seem to predispose to severe COVID-19.

Among the strengths of this study is its large sample size. We combined data from the Swedish Patient Register[19] and the ESPRESSO cohort[20] with data from 28 pathology departments and identified more than 67,000 patients with IBD. This yielded substantial statistical power and also allowed for important sub-analyses. While the aHRs of COVID-19 seem to be similar in men and women, hospital-admission for COVID-19 was rare in childhood IBD. During follow-up, less than one in 1000 patients with childhood IBD was admitted. However, since COVID-19 tends to be a mild disease in children,[41] this still translated into a 2.93 times increased risk for COVID-19 hospital admission, albeit not statistically significant. No patient with IBD diagnosed in

childhood was admitted to the intensive care unit or died from COVID-19. Our research group has earlier shown that childhood IBD is a risk factor for death from infections (HR = 6.3).[7] Most deaths in COVID-19 have however occurred in the elderly. We found a 23% increased risk of COVID-19 hospital admission for COVID-19 in IBD patients diagnosed at age 60 years or above.

We leveraged several nationwide registers with prospective records on COVID-19. Through the Swedish Intensive Care Register, covering Sweden's 83 nonneonatal intensive care units, we obtained data used for our composite outcome "severe COVID-19". Data on death dates (death ≤30 days postdiagnosis) were retrieved from the Total Population Register that records 93% of all deaths within 10 days, and the remaining deaths within 30 days.[23] Our exposure definition, IBD, required both a relevant ICD code and a histopathology code with inflammation. This definition has been used before[42] and has a positive predictive value of 95%.[21] Our findings of the highest incidence of severe COVID-19 in males and the elderly supports a high internal validity. Reporting of COVID-19 positive tests to the Public Health Agency is mandatory in Sweden.

While our COVID-19 specific ethical amendment came with limitations (we were only allowed to add death dates and COVID-19-data to the ESPRESSO cohort[20]), we were able to adjust for comorbidities until 2016 in our rematched cohort using a propensity-score model. This did not impact on our risk estimates more than marginally.

Our sibling analyses enabled us to minimize confounding from shared risk factors such as genetics and environmental factors. Despite being based on more than 23,000 individuals with IBD, the sibling analysis had limited power. This likely explains the lack of statistical significance despite an aHR of 1.25 for COVID-19 hospital admission, which appears consistent with the increased risk seen in our main analysis.

Our main limitation is the lack of data on medication[43] and IBD disease activity. We did not have data on endoscopy or faecal calprotectin. Other limitations include the lack of data on body mass index and smoking. These factors, especially body mass index (obesity) and hypertension, seem to be important risk factors for severe COVID-19.

Neither were we able to explore the risk of COVID-19 according to UC/CD/IBD-U subtypes. Finally, we had no individual-based data on precautions undertaken by Swedish IBD patients during the pandemic, or on intubation during ICU care.

CONCLUSION

In this cohort study of more 67,000 patients with IBD, we found a moderately increased risk of COVID-19 hospital admission but no increased risk of severe COVID-19.

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CONFLICT OF INTERESTS

Jonas F. Ludvigsson coordinates a study on behalf of the Swedish IBD quality register (SWIBREG), that has received funding from Janssen corporation. Tracey G. Simon has served as a consultant to Aetion, for work unrelated to this manuscript. Ola Olén has been PI on projects at Karolinska Institutet partly financed by investigator-initiated grants from Janssen and Ferring, and also repsort a grant from Pfizer in the context of a national safety monitoring program. None of those studies have any relation to the present study. Karolinska Institutet has received fees for lectures and participation on advisory boards from Janssen, Ferring, Takeda and Pfizer regarding topics not related to the present study. Jonas Halfvarson has served as an advisory board member, speaker or consultant for Abbvie, Celgene, Celltrion, Ferring, Hospira, Janssen, Meda, Medivir, MSD, Novartis, Olink proteomics, Pfizer, Prometheus Laboratories, Inc., Sandoz, Shire, Takeda, Thermo Fisher Scientific, Tillotts Pharma and Vifor Pharma, and received grant support from Janssen, MSD and Takeda. The other authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Guarantor, funding and writing first draft of the manuscript: Jonas F. Ludvigsson. *Acquisition of data*: Jonas F. Ludvigsson and Emma Larsson. *Analysis*: Jonas Söderling. *Study concept and design and critical revision of the manuscript for important intellectual content and approval of final version*: All coauthors.

DATA AVAILABILITY STATEMENT

No additional data are available due to Swedish regulations. Researchers can apply from the data through the Swedish National Board of Health and Welfare, and the government agency Statistics Sweden.

ETHICS APPROVAL

This study was approved by the Stockholm Ethics Review Board (no: 2014/1287-31/4, with a COVID-19 specific amendment: 2020-02307).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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