Risk of Upper Gastrointestinal Bleeding and Gastroduodenal Ulcers in Persons With Schizophrenia: A Danish Cohort Study

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INTRODUCTION: **There is little evidence about gastrointestinal (GI) disorders in patients with schizophrenia. We examined association of schizophrenia with upper GI bleeding (UGIB) and nonbleeding ulcers and associated risk factors and mortality.**

METHODS: **We used the data linked from population-based registries in Denmark. Among patients with incident schizophrenia in 1980–2011, we computed cumulative incidences and standardized incidence ratios of UGIB, bleeding ulcers, and nonbleeding ulcers compared with the general population; evaluated risk factors for the 3 GI endpoints, including somatic and psychiatric comorbidity; and examined subsequent all-cause mortality.**

RESULTS: **Among 39,998 patients with schizophrenia, the standardized incidence ratios were 2.92 (95% confidence interval (CI), 2.76–3.08) for UGIB, 2.36 (95% CI, 2.15–2.58) for bleeding ulcers, and 2.00 (95% CI, 1.87–2.15) for nonbleeding ulcers. Risk factors for UGIB and nonbleeding ulcers included age, somatic comorbidity, and medication use. UGIB and nonbleeding ulcers were associated with the subsequent increase in mortality.**

CONCLUSIONS: **Schizophrenia is associated with an increased risk of UGIB and nonbleeding ulcers, whose risk factors in patients with schizophrenia are similar to those in the general population.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A6 and http://links.lww.com/CTG/A12

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INTRODUCTION

Schizophrenia is a psychotic disorder characterized by delusions, hallucinations, disorganized speech and behavior, and other symptoms that cause social or occupational dysfunction. For its diagnosis, symptoms must have been present for 6 months and include at least 1 month of active symptoms (1). Diagnosis of schizophrenia is associated with a 12- to 20-year decrease in life expectancy, with a substantial proportion of the excess mortality attributable to somatic illness (2). Disorders of the digestive system seem to contribute to mortality due to treatable conditions, possibly through reluctance to seeking medical attention (3). Upper gastrointestinal bleeding (UGIB) is an acute or chronic hemorrhage emanating from the esophagus, stomach, or duodenum (4). The rate of hospital admission due to major UGIB events is 26–40 per 100,000 person-years (5). The most common conditions responsible for clinical nonvariceal UGIB are gastroduodenal ulcers, peptic or esophageal erosions, neoplasms, and Mallory-Weiss tears (6).

Few studies addressed the association between schizophrenia and nonvariceal UGIB, bleeding gastroduodenal ulcers, or nonbleeding gastroduodenal ulcers (7–9). An elevated risk in schizophrenia patients may be expected given the high-prevalent substance abuse (10). In this population-based cohort study, we examined whether the risks of UGIB and nonbleeding ulcers are greater among patients with schizophrenia than in the general population. Furthermore, we examined the risk factors for UGIB and nonbleeding ulcers among patients with schizophrenia. Finally, we examined survival following UGIB or nonbleeding ulcers among patients with schizophrenia.

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METHODS

Study design and setting

We conducted a historical cohort study using the linked data from the following population-based registries in Denmark: the Danish Civil Registration System, the Danish National Patient Registry (DNPR), the Danish Psychiatric Central Research Register (DPCRR), and the Danish National Health Services Prescription Database (11–14). Denmark's population was 5,122,065 on January 1, 1980, and 5,560,628 on January 1, 2011 (source: www.dst.dk). The Civil Registration System assigns unique personal identifiers to all Danish residents and tracks vital status and migration. The DNPR has recorded nonpsychiatric hospitalizations since 1977. The DPCRR has recorded admissions to psychiatric hospitals and to psychiatric wards within nonpsychiatric hospitals since 1968. Both DNPR and DPCRR have started tracking visits to emergency departments and hospital-based outpatient clinics since 1995. The Danish National Health Service Prescription Database tracks outpatient dispensings of all reimbursed prescriptions in outpatient pharmacies since 2004.

Study population

Our schizophrenia cohort consisted of patients with a first-time diagnosis of schizophrenia recorded in the DPCRR or the DNPR between January 1, 1980, and December 31, 2011, during inpatient stays or outpatient visits. Patients with a diagnosis of schizophrenia before 1980 were excluded. Patients were followed from the date of schizophrenia diagnosis until the date of an endpoint (described below), death, emigration, or December 31, 2012, whichever came first.

Endpoints

The 3 endpoints examined in this study were any UGIB, bleeding ulcers (a subset of UGIB), and nonbleeding ulcers. UGIB was defined as bleeding from esophagitis, gastric or duodenal ulcers, hematemesis, melena, or gastrointestinal (GI) bleeding with unspecified cause (15). Gastroduodenal ulcers were defined as ulcers within the stomach, duodenum, or involving an anastomosis in stomach surgery. The endpoints were identified from the DNPR using diagnostic codes from the International Classification of Diseases, Eighth Revision, through 1993 and Tenth Revision thereafter.

Potential risk factor for UGIB and nonbleeding ulcers

Data on potential risk factors for the endpoints among patients with schizophrenia were obtained using hospital diagnoses registered in the DNPR. We considered the following risk factors: nonbleeding conditions associated with esophagitis, gastritis, duodenitis, or Mallory-Weiss lesions; liver cirrhosis; esophageal varices, alcoholism-related disorders other than mental, behavioral, or and liver-related disorders; and somatic comorbidity, defined by the Charlson Comorbidity Index (CCI) scores (16). For the subset of patients diagnosed with schizophrenia starting in 2005 (to allow a minimum of 1 year of prescription history), we also obtained information on the use of prescription medications that may be associated with UGIB or for indications consistent with the underlying diseases that could increase the risk of the endpoints (6). The diagnoses recorded in the DPCRR and DNPR were used to capture psychiatric comorbidities, including affective disorders, substance use disorders, anxiety spectrum disorders, and personality disorders. The definitions of the study variables are listed in the Appendix (see Supplementary Digital Content 2, http://links.lww.com/CTG/A12).

Statistical analysis

For the schizophrenia cohort, we described demographic characteristics, baseline comorbidities, and baseline use of prescription medications. We used indirect standardization to compute standardized incidence ratios (SIRs) for the study endpoints as the ratio of the observed to the expected number of these events. The expected number of each study endpoint in the general Danish population was based on diagnoses recorded in the DNPR by sex, age in 5-year intervals, and calendar year of diagnosis in 5-year intervals. Incidence rates for each endpoint were computed after excluding patients with a given condition before the diagnosis of schizophrenia. Under this method, members of the general population contribute to follow-up time from entering the general population until outcome/exit of the study population or the end of study. The follow-up time is divided into sex, age, and calendar period strata in which incidence rates are computed and are used to obtain the expected number of outcomes among the patients with schizophrenia (17).

To examine the associations between potential risk factors and the study endpoints among the patients with schizophrenia, we computed, for each endpoint, a hazards ratio (HR) as a measure of relative risks, using Cox's proportional-hazards regression. Comorbidities and medication use were analyzed as time-varying variables. Crude and adjusted HRs associated with psychiatric and somatic comorbidities were computed for the patients in the schizophrenia cohort. Crude HRs associated with the use of prescription medication were computed for patients diagnosed with schizophrenia in 2005–2011, as the data on prescription dispensings were available from 2004 onward. Presence or absence of each potential risk factor was analyzed as a time-varying variable. Analyses were repeated disregarding the history of using proton pump inhibitors or H_2-receptor antagonists, since those may be markers of precursors to upper GI bleeding.

To examine mortality subsequent to the study endpoints, we created three subcohorts on the basis of the presence of each of the three endpoints following the schizophrenia diagnosis. For each member of a subcohort defined by the presence of an endpoint, we sampled up to 10 sex-matched and birth-year-matched schizophrenia patients from the underlying schizophrenia cohort from those who were alive and free from UGIB, bleeding ulcer, and nonbleeding ulcer, as appropriate on the date of the endpoint diagnosis. Within each subcohort, we constructed Kaplan-Meier curves to compute cumulative survival after each study endpoint, comparing schizophrenia patients with and without the study endpoint. We computed crude mortality rates and used Cox's proportional-hazards regression to estimate mortality rate ratios associated with each study endpoint, adjusting for the covariates. All estimates were computed with Poisson confidence intervals (CIs) using Byar's approximation unless the observed number of events was <10, in which case exact 95% CIs were computed. The analyses were conducted using SAS software.

This study received approval by the Danish Data Protection Agency (record number 2015-57-0002), which is required for all research. Danish law does not require ethics/institutional review board approval for the studies solely based on routine registry data.

Table 1. Distribution of baseline characteristics of 39,998 patients with a first-time diagnosis of schizophrenia in Denmark, 1980-2011

Characteristic	N (%)
Total, n (%)	39,998 (100)
Sex, n (%)	
Women	17,143 (42.9)
Men	22,855 (57.1)
Age at schizophrenia diagnosis, n (%)	
<20 yr	3682 (9.2)
20–35 yr	18,730 (46.8)
>35 yr	17,586 (44.0)
Calendar period of schizophrenia diagnosis, n (%)	
1980–1994	13,862 (34.7)
1995–2011	26,136 (65.3)
Psychiatric comorbidity, n (%)	
Depression	6,294 (15.7)
Mental, behavioral disorders due to the use of alcohol	6,334 (15.8)
Mental, behavioral disorders due to the use of substances other than alcohol	5,571 (13.9)
Schizoaffective disorders	16,190 (40.5)
Bipolar disorder	1,903 (4.8)
Other affective disorders	7,827 (19.6)
Anxiety disorders	3,311 (8.3)
Post-traumatic stress disorder	489 (1.2)
Organic mental disorders	3,238 (8.1)
Personality disorders	10,388 (26.0)
Other and unspecified mental disorders	11,519 (28.8)
Somatic comorbidity, n (%)	
Charlson Comorbidity Index score	
Low (score of 0—no comorbidity)	34,514 (86.3)
Medium (score of 1–2)	4,665 (11.7)
High (score of 3+)	819 (2.0)
Nonbleeding conditions, including esophagitis, gastritis, duodenitis, or Mallory-Weiss lesions	1,437 (3.6)
Liver cirrhosis	382 (1.0)
Esophageal varices	26 (0.1)
Use of prescription medications, n (%)[a]	
Known to cause ulcer or bleeding	
Antithrombotics	576 (1.4)
Aspirin 75–150 mg	460 (1.2)
Aspirin 100–500 mg	133 (0.3)
Nonaspirin NSAIDs	4,342 (10.8).
Indicative of UGIB risk factors	
Glucocorticoids	632 (1.5)
Proton pump inhibitors	2,108 (5.3)
H2-antagonists	425 (1.1)
Indicative of psychiatric comorbidity	
Selective serotonin reuptake inhibitors	4,663 (11.6)
Antidepressants	3,175 (7.9)
Antipsychotics (atypical)	5,243 (13.1)
Antipsychotics (other)	4,010 (10.0)
Anticonvulsants	1,509 (3.8)

NSAID, nonsteroidal anti-inflammatory drug; UGIB, upper gastrointestinal bleeding.
[a]Data from 2003 onward.

RESULTS

The schizophrenia cohort

During the study period, we identified 39,998 patients with a first-time diagnosis of schizophrenia recorded in the DPCRR. A majority (57%) of the patients were men and 56% were younger than 35 years at schizophrenia diagnosis. Table 1 shows prevalence of comorbid psychiatric disorders, substance use disorders, and somatic comorbidity in the schizophrenia cohort.

Rates of the endpoints

During 459,564 person-years of follow-up, 1,264 incident cases of UGIB were diagnosed. Median follow-up for all types of UGIB was 10.3 years (interquartile range: 4.6–17.1 years). The cumulative incidence of UGIB after schizophrenia diagnosis was 0.37% (95% CI, 0.31%–0.43%) after 1 year of follow-up, 2.30% (95% CI, 2.14%–2.47%) after 10 years, and 4.26% (95% CI, 4.01%–4.53%) after 20 years of follow-up. There were 459 incident cases of bleeding gastroduodenal ulcers during 467,394 years of follow-up. The median follow-up time for bleeding ulcers was 10.4 years (interquartile range: 4.6–17.1 years). The cumulative incidence of bleeding ulcers was 0.13% (95% CI, 0.09%–0.17%) after 1 year of follow-up, 0.77% (95% CI, 0.68–0.87) after 10 years, and 1.57% (95% CI, 1.41%–1.74%) after 20 years of follow-up. Finally, there were 808 incident cases of nonbleeding gastroduodenal ulcers during 461 132 years of follow-up. The cumulative incidence of nonbleeding ulcers was 0.25% (95% CI, 0.20%–0.30%) after 1 year of follow-up, 1.53% (95% CI, 1.40%–1.67%) after 10 years, and 2.80% (95% CI, 2.59%–3.02%) after 20 years of follow-up. In absolute terms, the risk for all three outcomes ranged between 1 in 24 patients and 1 in 64 patients affected over 20 years.

Among patients with schizophrenia, the overall SIRs were 2.92 (95% CI, 2.76–3.08) for UGIB, 2.36 (95% CI, 2.15–2.58) for bleeding ulcers, and 2.00 (95% CI, 1.87–2.15) for nonbleeding ulcers. The SIRs for the 3 study endpoints did not differ by sex and were fairly stable across strata of age, and calendar year at schizophrenia diagnosis. The SIRs in the first year following the schizophrenia diagnosis were slightly greater than those during subsequent years for all endpoints (Table 2).

Table 2. Observed and expected cases and SIRs of UGIB, bleeding ulcers, and nonbleeding ulcers among patients with schizophrenia

Variable	Observed (O)	Person-years at risk	Expected (E)	SIR (O/E) (95% CI)
UGIB				
Total incident cases	1,264	459,564	433.0	2.92 (2.76–3.08)
Sex				
Female	513	195,977	190.4	2.69 (2.47–2.94)
Male	751	263,587	242.7	3.09 (2.88–3.32)
Age at schizophrenia diagnosis				
<20 yr	55	40,687	13.2	4.16 (3.13–5.41)
20–35 yr	460	241,052	119.3	3.86 (3.51–4.22)
>35 yr	749	177,824	300.5	2.49 (2.32–2.68)
Calendar period of schizophrenia diagnosis				
1980–1994	630	251,366	249.1	2.53 (2.34–2.73)
1995–2011	634	208,198	184.0	3.45 (3.18–3.72)
Follow-up length				
0–1 yr	231	74,776	54.9	4.21 (3.68–4.79)
2–10 yr	581	236,486	198.2	2.93 (2.70–3.18)
11–20 yr	322	115,357	128.8	2.50 (2.23–2.79)
21–32 yr	130	32,944	51.1	2.54 (2.12–3.02)
Bleeding ulcers				
Total incident cases	459	467,394	194.7	2.36 (2.15–2.58)
Sex				
Female	196	198,939	91.0	2.15 (1.86–2.48)
Male	263	268,454	103.7	2.54 (2.24–2.86)
Age at schizophrenia diagnosis				
<20 yr	6	41,118	3.0	2.00 (0.73–4.36)
20–35 yr	135	244,807	39.3	3.44 (2.88–4.07)
>35 yr	318	181,468	152.4	2.09 (1.86–2.33)
Calendar year of schizophrenia diagnosis				
1980–1994	261	254,741	118.9	2.20 (1.94–2.48)
1995–2011	198	212,653	75.8	2.61 (2.26–3.00)
Follow-up length				
0–1 yr	75	75,723	24.4	3.08 (2.42–3.86)
2–10 yr	206	240,464	88.6	2.32 (2.02–2.66)
11–20 yr	130	117,555	58.4	2.23 (1.86–2.64)
21–32 yr	48	33,652	23.2	2.06 (1.52–2.73)
Nonbleeding ulcers				
Total incident cases	808	461,132	403.3	2.00 (1.87–2.15)
Sex				
Female	383	196,211	194.8	1.97 (1.77–2.17)
Male	425	264,920	208.6	2.04 (1.85–2.24)
Age at schizophrenia diagnosis				
<20 yr	34	40,946	11.4	2.99 (2.07–4.18)
20–35 yr	267	242,630	117.8	2.27 (2.00–2.56)
>35 yr	507	177,555	274.1	1.85 (1.69–2.02)
Calendar year of schizophrenia diagnosis				
1980–1994	448	252,099	256.8	1.74 (1.59–1.91)
1995–2011	360	209,033	146.5	2.46 (2.21–2.72)
Follow-up length				
0–1 yr	165	74,889	56.7	2.91 (2.48–3.39)
2–10 yr	378	237,129	194.8	1.94 (1.75–2.15)
11–20 yr	204	115,872	114.8	1.78 (1.54–2.04)
21–32 yr	61	33,241	37.0	1.65 (1.26–2.12)

CI, confidence interval; SIR, standardized incidence ratio; UGIB, upper gastrointestinal bleeding.

Risk factors for the endpoints among patients with schizophrenia

Table 3 shows the results of our analysis of risk factors for UGIB among patients with schizophrenia. Even moderately increased medical comorbidity, such as a CCI score of 1 or 2, was associated with increased risk (adjusted HR = 2.46, 95% CI, 2.16–2.80). Schizophrenia diagnosis after age 35 years was a strong risk factor (adjusted HR = 2.32, 95% CI, 1.75–3.08). Psychological or behavioral disorders associated with use of alcohol (adjusted HR = 1.63, 95% CI, 1.41–1.87) and other substances (adjusted HR = 1.25, 95% CI, 1.09–1.44) also were associated with increased risk. Certain medications were also risk factors for UGIB (Table 3). Aside from organic brain syndromes (adjusted HR = 1.21, 95% CI, 1.05–1.40), comorbid mood or anxiety disorders were not associated with increased risk following accounting for other potential risk factors.

Patients older than 35 years at schizophrenia diagnosis were more likely to have experienced bleeding ulcers than patients who were younger than 20 years at diagnosis (adjusted HR = 8.50, 95% CI, 3.76–19.17). Other risk factors included anxiety disorders (adjusted HR = 1.37, 95% CI, 1.05–1.80), prior nonbleeding conditions of the upper GI tract (adjusted HR = 2.48, 95% CI, 1.94–3.17), and presence of somatic comorbidity (adjusted HR for a medium CCI score = 3.30, 95% CI, 2.67–4.07).

Table 3. Crude[a] and adjusted[b] HRs for UGIB, bleeding ulcers, and nonbleeding ulcers according to the presence of various risk factors, assessed as time-varying variables when appropriate, among patients with schizophrenia in Denmark, 1980–2011

Comparison	UGIB, HR (95% CI)		Bleeding ulcer, HR (95% CI)		Nonbleeding ulcer, HR (95% CI)	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Women vs men	0.92 (0.82–1.03)	0.85 (0.75–0.96)	1.01 (0.84–1.21)	0.82 (0.67–1.00)	1.22 (1.06–1.40)	1.12 (0.96–1.29)
Age at schizophrenia diagnosis: 20–35 yr vs <20 yr	1.43 (1.08–1.89)	1.22 (0.92–1.61)	3.79 (1.68–8.60)	3.24 (1.43–7.36)	1.34 (0.94–1.91)	1.21 (0.85–1.73)
Age at schizophrenia diagnosis: >35 yr vs <20 yr	3.23 (2.46–4.25)	2.32 (1.75–3.08)	12.57 (5.60–28.19)	8.50 (3.76–19.17)	3.48 (2.46–4.92)	2.76 (1.93–3.93)
Calendar period at schizophrenia diagnosis: 1995–2011 vs 1980–1994	1.42 (1.25–1.62)	1.00 (0.87–1.14)	1.03 (0.83–1.27)	0.76 (0.61–0.95)	0.94 (0.80–1.09)	0.67 (0.56–0.79)
Psychiatric comorbidity (present vs absent, time-varying)						
Depression	1.36 (1.19–1.55)	0.85 (0.69–1.05)	1.36 (1.10–1.69)	0.97 (0.67–1.40)	1.22 (1.03–1.45)	0.96 (0.72–1.28)
Mental, behavioral disorders due to the use of alcohol	2.75 (2.46–3.08)	1.63 (1.41–1.87)	1.86 (1.54–2.26)	1.14 (0.89–1.47)	2.07 (1.79–2.39)	1.24 (1.03–1.50)
Mental, behavioral disorders due to the use of substances other than alcohol	1.87 (1.65–2.10)	1.25 (1.09–1.44)	1.26 (1.02–1.57)	1.07 (0.83–1.37)	1.67 (1.44–1.95)	1.39 (1.16–1.65)
Schizoaffective disorders	1.32 (1.18–1.48)	1.10 (0.97–1.23)	1.06 (0.88–1.27)	0.95 (0.78–1.15)	1.10 (0.96–1.26)	0.94 (0.81–1.09)
Bipolar disorder	1.32 (1.10–1.59)	1.00 (0.82–1.23)	1.28 (0.94–1.74)	0.94 (0.67–1.32)	1.17 (0.92–1.50)	0.90 (0.69–1.17)
Other affective disorders	1.52 (1.35–1.71)	1.17 (0.97–1.42)	1.43 (1.17–1.75)	1.05 (0.75–1.47)	1.27 (1.09–1.49)	0.91 (0.70–1.18)
Anxiety disorders	1.66 (1.42–1.94)	1.07 (0.91–1.27)	1.80 (1.39–2.31)	1.37 (1.05–1.80)	1.68 (1.38–2.04)	1.19 (0.97–1.47)
Post-traumatic stress disorder	1.42 (0.90–2.24)	1.18 (0.75–1.87)	0.41 (0.10–1.66)	0.37 (0.09–1.50)	2.16 (1.37–3.41)	2.04 (1.29–3.25)
Organic mental disorders	1.87 (1.63–2.14)	1.21 (1.05–1.40)	1.72 (1.37–2.17)	1.28 (1.00–1.64)	1.76 (1.48–2.09)	1.18 (0.98–1.42)
Personality disorders	1.45 (1.30–1.62)	1.03 (0.91–1.17)	1.24 (1.03–1.49)	1.05 (0.84–1.30)	1.45 (1.26–1.67)	1.14 (0.97–1.34)
Other and unspecified mental disorders	1.52 (1.36–1.70)	1.11 (0.98–1.26)	1.08 (0.89–1.30)	0.91 (0.73–1.12)	1.43 (1.24–1.64)	1.20 (1.03–1.41)
Somatic comorbidity (present vs absent, time-varying)						
Nonbleeding conditions including esophagitis, gastritis, duodenitis, or Mallory-Weiss lesions	4.83 (4.20–5.55)	2.53 (2.18–2.94)	4.59 (3.66–5.76)	2.48 (1.94–3.17)	4.46 (3.73–5.33)	2.62 (2.15–3.18)
Liver cirrhosis	4.85 (3.79–6.20)	1.24 (0.96–1.62)	4.93 (3.34–7.27)	1.29 (0.84–1.98)	4.65 (3.42–6.32)	1.34 (0.96–1.89)
Esophageal varices	17.55 (9.11–33.83)	2.20 (1.11–4.36)	17.56 (7.85–39.30)	2.40 (0.99–5.79)	12.09 (5.74–25.44)	1.54 (0.69–3.43)
Alcoholism-related disorders other than mental, behavioral, or liver-related disorders	3.19 (2.77–3.66)	1.35 (1.14–1.59)	2.47 (1.93–3.16)	1.21 (0.89–1.64)	2.71 (2.26–3.25)	1.31 (1.04–1.63)
CCI score						
1–2 (medium) vs 0 (low)	3.57 (3.16–4.03)	2.46 (2.16–2.80)	4.67 (3.83–5.70)	3.30 (2.67–4.07)	3.09 (2.65–3.60)	2.17 (1.85–2.56)
3+ (high) vs 0 (low)	7.38 (6.22–8.75)	3.65 (3.02–4.42)	7.86 (5.91–10.45)	3.81 (2.76–5.26)	5.34 (4.22–6.76)	2.67 (2.05–3.48)
Use of prescription medication (yes vs no, time-varying)						
Aspirin 75–150 mg	2.78 (1.64–4.70)		4.52 (1.98–10.34)		5.28 (2.92–9.54)	

Table 3. (*continued*)

Comparison	UGIB, HR (95% CI)		Bleeding ulcer, HR (95% CI)		Nonbleeding ulcer, HR (95% CI)	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Aspirin 100–500 mg	3.38 (1.38–8.27)		2.23 (0.31–16.30)		1.27 (0.18–9.12)	
Nonaspirin NSAIDs	1.79 (1.25–2.56)		1.84 (0.94–3.61)		1.84 (1.12–3.03)	
Glucocorticoids	1.54 (0.87–2.74)		0.77 (0.19–3.21)		1.88 (0.90–3.94)	
Proton pump inhibitors	4.04 (2.84–5.77)		6.94 (3.40–14.18)		3.81 (2.34–6.22)	
H2-antagonists	1.93 (1.01–3.69)		2.73 (0.96–7.72)		2.31 (1.00–5.34)	
Selective serotonin reuptake inhibitors	1.37 (0.96–1.95)		1.25 (0.65–2.42)		1.37 (0.84–2.24)	
Antidepressants	1.35 (0.95–1.92)		1.87 (0.97–3.60)		1.23 (0.75–2.01)	
Antipsychotics (atypical)	1.50 (0.95–2.37)		0.99 (0.46–2.14)		0.81 (0.47–1.40)	
Antipsychotics (other)	2.55 (1.72–3.79)		1.97 (0.97–3.99)		1.64 (0.99–2.73)	
Antithrombotics	2.69 (1.65–4.38)		4.95 (2.32–10.54)		4.96 (2.82–8.71)	
Anticonvulsants	2.31 (1.60–3.33)		2.54 (1.29–5.00)		2.51 (1.52–4.15)	

CI, confidence interval; CCI, Charlson Comorbidity Index; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug; UGIB, upper gastrointestinal bleeding.
[a]Crude MRR for medications restricted to the persons diagnosed with schizophrenia starting in 2005; adjusted MRRs for medications are not estimated.
[b]Adjusted for all somatic and psychiatric comorbidity in the model. The data on medication are not included as they were not available during the entire period.

Risk factors for nonbleeding ulcers were generally similar to those for bleeding ulcers (Table 3).

Mortality and the study endpoints in patients with schizophrenia

The overall mortality rate per 100 person-years was 8.79 (95% CI, 8.11–9.50) following UGIB, 10.17 (95% CI, 8.99–11.46) following bleeding ulcers, and 6.85 (95% CI, 6.18–7.57) following nonbleeding ulcers. Compared with schizophrenia patients who did not experience a given endpoint, affected patients had increased mortality: The adjusted mortality rate ratios were 1.85 (95% CI, 1.67–2.04) for UGIB, 1.75 (95% CI, 1.51–2.04) for bleeding ulcers, and 1.43 (95% CI, 1.26–1.62) for nonbleeding ulcers (Table 4; see Figures, Supplementary Digital Content 1, http://links.lww.com/CTG/A6). Alcohol and other substance use disorders were risk factors for mortality following all 3 study endpoints, as was the presence of comorbidity (Table 4). Anticoagulants and antithrombotic agents were associated with increased mortality following the study endpoints.

DISCUSSION

In this cohort study with up to 32 years of follow-up, we observed an increase in the incidence rate of UGIB, the bleeding ulcers, and nonbleeding ulcers in patients with schizophrenia compared with members of the general population of the same sex and similar age. Risk factors for the endpoints included older age at schizophrenia diagnosis, somatic comorbidity, indicators of alcohol abuse, and the use of antithrombotic and anticonvulsant medications. These are similar to the risk factors identified in the general population (6). Each of the 3 study endpoints was associated with approximately 10% all-cause mortality in the year following the diagnosis of the endpoint.

Findings of this study are consistent with the considerably increased medical comorbidity and shortened life expectancy documented for schizophrenia (2). The association between schizophrenia and ulcers, seen in our study, has not been shown by all available evidence. In cohort study based on insurance claims in Taiwan, schizophrenia was associated with a 27-percent higher risk of peptic ulcer compared with the general population after adjustment, but the association was no longer present after controlling for use of medications, including analgesics and nervous system medications (8). A hospital-based case-control study in the United States comparing the cases of schizophrenia with controls on the prevalence of peptic ulcers reported an inverse association between schizophrenia and peptic ulcer, although, by design, the study estimated the risk of schizophrenia in patients with vs without ulcers, not *vice versa* (9). The differences in observations may stem from greater risks of the outcomes in the comparator groups of the 2 studies (contributors of insurance claims (8) and hospitalized patients (8), respectively). In our analysis, the association did not change after inclusion, from 1995 onward, of the diagnoses recorded at hospital outpatient clinics, in addition to the diagnoses recorded at hospitalizations. The previously described risk factors for increased rates of these conditions in the general population were observed among patients with schizophrenia in our study. A nonpopulation-based study in the United States found moderately elevated rates of the study outcomes (7). Increased rates of UGIB have been observed in association with a generally high burden of medical disease (18). The use of nonsteroid anti-inflammatory drugs (NSAIDs), alcohol, and tobacco is increased in persons with schizophrenia, and these agents' etiologic roles in gastroduodenal ulcer have been well-described (19). The use of certain medications may indicate the underlying conditions that increase the risk for UGIB. Glucocorticoids and SSRIs may potentiate the effect of NSAIDs or aspirin in causing gastroduodenal ulcers (20). Increases in the risk associated with the various psychiatric medications could indicate an effect of increased psychiatric comorbidity or simply increased severity of the primary exposure, schizophrenia. The relative risk increase associated with low-dose aspirin, however, was similar in the patients with schizophrenia (2.8) and in the general population (2.6) (6). The estimated relative increases in risk were lower in patients with schizophrenia in

Table 4. Crude[a] and adjusted[b] MRRs subsequent to UGIB, bleeding ulcers, and nonbleeding ulcers among patients with schizophrenia in Denmark (1980-2011)

Risk factor present before index date	UGIB, MRR (95% CI)		Bleeding ulcers, MRR (95% CI)		Non-bleeding ulcers, MRR (95% CI)	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
GI event cohort vs GI event-free comparison cohort	2.22 (2.02–2.45)	1.85 (1.67–2.04)	2.14 (1.85–2.47)	1.75 (1.51–2.04)	1.72 (1.52–1.93)	1.43 (1.26–1.62)
Psychiatric comorbidity (present vs absent, time-independent)						
Depression	1.02 (0.93–1.12)	0.78 (0.67–0.92)	1.17 (1.03–1.34)	0.81 (0.64–1.03)	1.13 (1.02–1.26)	0.97 (0.80–1.18)
Mental, behavioral disorders due to the use of alcohol	1.83 (1.68–1.99)	1.45 (1.31–1.62)	1.77 (1.56–2.02)	1.34 (1.13–1.58)	1.93 (1.74–2.13)	1.48 (1.30–1.68)
Mental, behavioral disorders due to the use of substances other than alcohol	1.86 (1.67–2.07)	1.42 (1.26–1.60)	2.04 (1.72–2.42)	1.49 (1.23–1.81)	2.11 (1.86–2.40)	1.53 (1.32–1.77)
Schizoaffective disorders	1.03 (0.96–1.11)	0.94 (0.87–1.02)	1.03 (0.92–1.15)	0.95 (0.85–1.06)	1.09 (1.00–1.19)	0.99 (0.91–1.09)
Bipolar disorder	1.10 (0.97–1.24)	1.10 (0.96–1.27)	1.21 (1.02–1.45)	1.16 (0.94–1.43)	1.21 (1.05–1.39)	1.19 (1.01–1.40)
Other affective disorders	1.11 (1.02–1.21)	1.19 (1.03–1.36)	1.24 (1.10–1.40)	1.28 (1.04–1.58)	1.13 (1.02–1.25)	0.98 (0.82–1.16)
Anxiety disorders	1.02 (0.89–1.18)	0.85 (0.73–0.99)	1.13 (0.93–1.38)	0.93 (0.75–1.15)	1.26 (1.08–1.48)	1.03 (0.87–1.22)
Post-traumatic stress disorder	0.69 (0.33–1.44)	0.63 (0.30–1.32)	0.83 (0.35–1.94)	0.84 (0.36–2.00)	0.83 (0.36–1.92)	0.77 (0.33–1.80)
Organic mental disorders	1.43 (1.29–1.57)	1.10 (0.99–1.22)	1.51 (1.31–1.74)	1.16 (1.00–1.36)	1.56 (1.39–1.75)	1.21 (1.07–1.37)
Personality disorders	1.09 (1.00–1.19)	0.84 (0.77–0.93)	1.13 (0.99–1.28)	0.83 (0.72–0.97)	1.17 (1.06–1.29)	0.89 (0.80–1.00)
Other and unspecified mental disorders	1.26 (1.16–1.37)	1.09 (1.00–1.19)	1.21 (1.07–1.37)	0.96 (0.84–1.10)	1.30 (1.18–1.44)	1.03 (0.93–1.15)
Somatic comorbidity (present vs absent, time-independent)						
Nonbleeding conditions including esophagitis, gastritis, duodenitis, or Mallory-Weiss lesions	1.38 (1.21–1.59)	0.92 (0.79–1.06)	1.32 (1.09–1.60)	0.87 (0.71–1.07)	1.36 (1.14–1.62)	0.90 (0.74–1.08)
Liver cirrhosis	2.53 (2.01–3.18)	1.08 (0.84–1.38)	3.32 (2.30–4.77)	1.67 (1.13–2.49)	2.63 (2.02–3.42)	1.28 (0.96–1.70)
Esophageal varices	8.31 (3.37–20.50)	2.20 (0.86–5.61)	3.43 (1.32–8.86)	0.87 (0.32–2.38)	3.07 (1.27–7.43)	0.77 (0.30–1.97)
Alcoholism-related disorders other than mental, behavioral, or liver-related disorders	1.89 (1.68–2.13)	1.14 (0.99–1.31)	2.11 (1.77–2.52)	1.34 (1.07–1.66)	1.97 (1.72–2.26)	1.13 (0.96–1.34)
CCI score						
1–2 (medium) vs 0 (low)	1.82 (1.67–1.99)	1.61 (1.48–1.76)	1.95 (1.73–2.21)	1.73 (1.53–1.97)	1.79 (1.62–1.98)	1.59 (1.43–1.77)
3+ (high) vs 0 (low)	2.86 (2.50–3.26)	2.36 (2.05–2.72)	2.74 (2.24–3.35)	2.25 (1.82–2.79)	3.03 (2.55–3.59)	2.57 (2.15–3.08)
Use of prescription medication (yes vs no, time-independent)						
Aspirin 75–150 mg	1.50 (1.26–1.79)		1.31 (0.99–1.75)		1.47 (1.14–1.90)	
Aspirin 100–500 mg	1.26 (0.96–1.67)		1.64 (1.07–2.51)		1.31 (0.87–1.97)	
Nonaspirin NSAIDs	1.27 (1.10–1.47)		1.14 (0.90–1.44)		1.03 (0.82–1.27)	
Glucocorticoids	1.67 (1.31–2.13)		1.05 (0.67–1.66)		1.22 (0.86–1.75)	
Proton pump inhibitors	1.45 (1.24–1.70)		1.41 (1.09–1.82)		1.34 (1.06–1.68)	
H2-antagonists	0.94 (0.67–1.31)		0.82 (0.48–1.40)		1.33 (0.87–2.02)	
SSRIs	1.13 (0.97–1.32)		1.18 (0.92–1.51)		1.09 (0.86–1.37)	
Antidepressants	1.10 (0.93–1.30)		1.08 (0.83–1.41)		1.27 (1.00–1.60)	
Antipsychotics (atypical)	1.22 (1.05–1.41)		1.09 (0.86–1.38)		1.08 (0.87–1.35)	
Antipsychotics (other)	1.26 (1.08–1.46)		1.27 (1.00–1.61)		1.10 (0.89–1.36)	

Table 4. (*continued*)

Risk factor present before index date	UGIB, MRR (95% CI)		Bleeding ulcers, MRR (95% CI)		Non-bleeding ulcers, MRR (95% CI)	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Antithrombotics	1.64 (1.39–1.93)		1.45 (1.11–1.89)		1.57 (1.23–2.01)	
Oral hypoglycemic agents	1.29 (1.04–1.61)		1.65 (1.17–2.33)		1.37 (0.96–1.94)	
Anticonvulsants	1.74 (1.48–2.05)		1.57 (1.19–2.05)		1.48 (1.15–1.90)	

CI, confidence interval; CCI, Charlson Comorbidity Index; GI, gastrointestinal; MRR, mortality rate ratio; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor; UGIB, upper gastrointestinal bleeding.
[a]Crude MRR for medications restricted to the persons diagnosed with schizophrenia starting in 2005; adjusted MRRs for medications are not estimated.
[b]Adjusted for all somatic and psychiatric comorbidity in the model. The data on medication are not included as they were not available during the entire period.

our study than those reported in the similar general population, for example, 1.8 vs 2.4 to 2.0 for nonaspirin NSAIDs (21); 2.7 vs 4.0 for antithrombotics (22); and 1.4 vs 3.6 for SSRIs (23). The differences are likely explainable by the greater background risk in the schizophrenia population, as shown in this study. Another explanation for greater risk of UGIB and increased associated mortality is potential reluctance of schizophrenia patients to seek medical attention and poor compliance to medical treatment (24).

A direct biologic effect of schizophrenia on gastroduodenal ulcers and UGIB seems less likely, but cannot be excluded. Schizophrenia has been associated with effects on coagulation, although most evidence suggests prothrombotic effects. Evidence is conflicting as to whether such effects stem from schizophrenia, its treatment, or obesity due to treatment (25,26). Little is known about the association between schizophrenia and increased ulcer formation. Elevated dopaminergic activity is thought to have a protective effect on ulcer formation (27). Another possible explanations of greater risks of UGIB and nonbleeding ulcers in patients with schizophrenia are elevated rates of *Helicobacter pylori* positivity (28).

Residents of Denmark enjoy universal health care, which is combined with a large array of registries and medical databases (including the oldest population-based psychiatric registry), linkable using unique individual identifiers, thus permitting virtually lifelong follow-up of all residents and much of their medical history. This study was large, allowing good statistical precision of risk estimates. In addition, the inclusion of the entire population of Denmark eliminated selection bias. Finally, misdiagnosis of schizophrenia is unlikely, based on the prior validation of diagnoses in the DPCRR (29). The diagnosis of UGIB in the Danish National Patient Register has a positive predictive value of 77% (30). Analyses based on health and administrative population-based registries are limited to routinely recorded data, potentially omitting important clinical details. The detection of UGIB or nonbleeding gastroduodenal ulcers within the healthcare system is dependent on the severity of symptoms and both entities can go clinically unrecognized (31). Their incidental discovery on endoscopy is likely among patients with schizophrenia who have regular contact with the health system, but prior studies have found decreased utilization of surgical procedures among patients with schizophrenia (32). Finally, the observed associations may be partially due to residual confounding by unmeasured or imprecise characteristics, for example, by socioeconomic status, associated both with schizophrenia and with ulcer diseases, (33) by smoking or by medication use (8).

The magnitude of our estimate may be different in communities in which patients with schizophrenia have limited access to medical or psychiatric care. Because Denmark is a country with a universal healthcare system, including mental health services, somatic comorbidity among patients with schizophrenia may be lower or less severe than in other settings. Thus, the association between schizophrenia and GI bleeding may be weaker in Denmark than in counties with more limited services. As our study measured effects at a population level, care also should be taken in generalizing our findings to clinical or institutional facilities that select patients requiring medical or psychiatric care, as the patients may differ in terms of disease severity and distribution of risk factors.

CONFLICTS OF INTEREST

Guarantor of the article: Vera Ehrenstein, DSc.

Specific author contributions: C.C.C. led the writing and participated in data analysis and interpretation. D.K.F. participated in planning of data analyses; conducted the analyses and revised the manuscript for intellectual contents. N.F. participated in planning and conducting the study and interpretation of the results, and revised the manuscript for intellectual contents. H.T.S. participated in planning and conducting the study, provided clinical expertise, interpreted the data, and revised the manuscript for intellectual contents. S.M.-R. and B.B. provided clinical expertise, interpreted the data, and revised the manuscript for intellectual contents. V.E. participated in planning and conducting the study, supervised data analyses, and revised the manuscript for intellectual contents. All authors approved the final version of the article, including the authorship list.

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Potential competing interests: B.B. and S.M.-R. are employees of Roche. N.F. is a former employee of Roche and is currently employed by UCB. D.F., H.T.S., and V.E. are employees of Aarhus University or Aarhus University Hospital. Roche's employees collaborated on and coauthored the manuscript. The academic institution of the corresponding author retained unrestricted right to publish the findings.

Study Highlights

WHAT IS KNOWN

- ✓ Schizophrenia is associated with a decreased life expectancy, partially attributable to somatic illness.
- ✓ UGIB and nonbleeding ulcers as well as subsequent mortality have not been extensively studied among patients with schizophrenia.

WHAT IS NEW HERE

- ✓ Patients with schizophrenia have a higher risk of UGIB and nonbleeding ulcers than the general population of the same age and sex.
- ✓ Among patients with schizophrenia, the presence of these conditions is associated with increased all-cause mortality.

TRANSLATIONAL IMPACT

- ✓ Results of this study may be useful to the clinicians treating somatic illness in patients with schizophrenia.

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