Association of Relapse With All-Cause Mortality in 32,071 Adults With Stable Schizophrenia: A Longitudinal Commercial and Medicare Database Study

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Introduction

- Schizophrenia shortens life expectancy by an estimated 15 years[1,2]
- Excess mortality in schizophrenia arises from multiple sources, including the following[3]:
  - Suicide and other non-natural causes
  - Organ system (eg, endocrine, respiratory, gastrointestinal, urogenital, neurologic, cardiovascular, hepatic, and cerebrovascular) disease/dysfunction or cancer
- Increased mortality is observed early in the course of disease[3,4]
- Mortality risk is influenced by modifiable factors such as lifestyle behaviors, access to care, and use of antipsychotic medication[3]
  - Switching from an oral antipsychotic (OAP) to a long-acting injectable (LAI) antipsychotic early in the course of disease is associated with lower mortality risk[5]
  - LAI antipsychotics are also associated with a reduced risk for relapse[6,7]
- Relapse adversely affects outcomes for patients with schizophrenia,[8] yet its influence on mortality is not well characterized

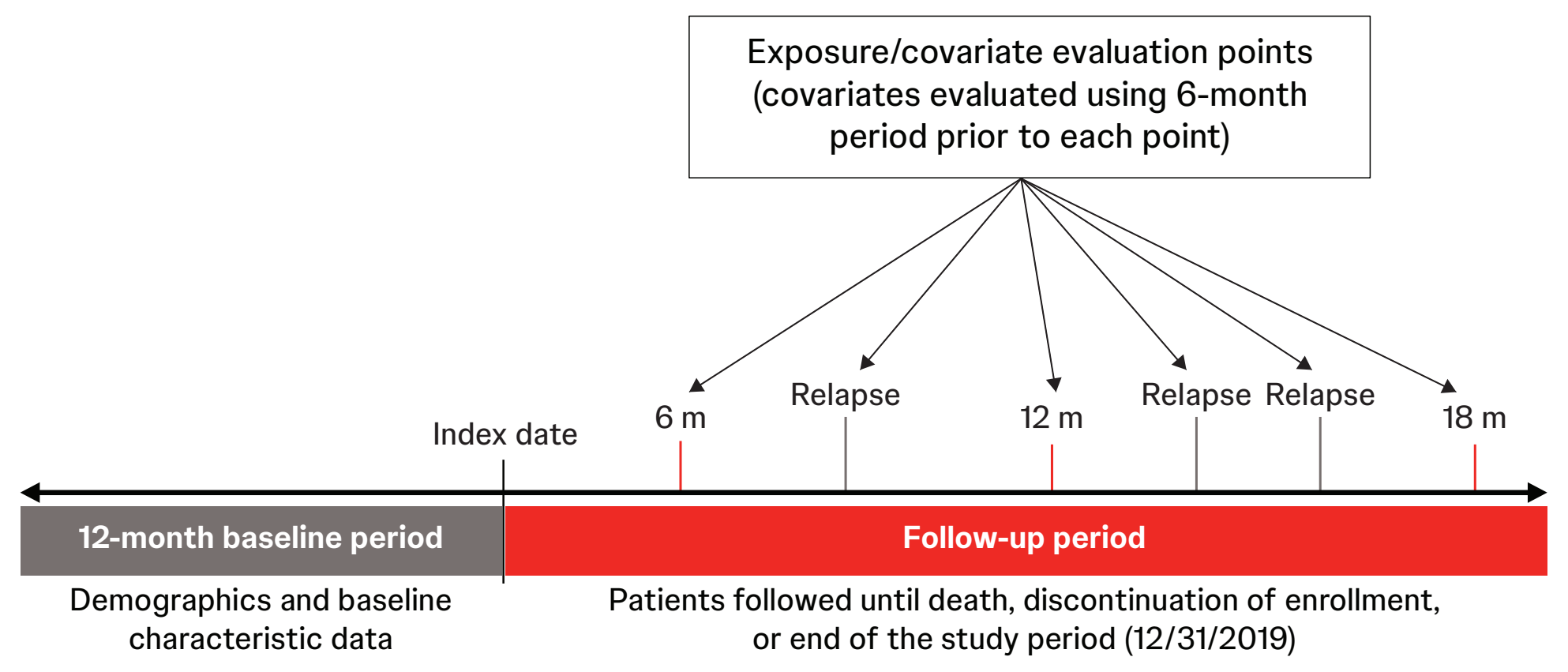
Objective

- To determine whether relapse independently increases all-cause mortality risk in patients with stable schizophrenia

Methods

- This longitudinal, non-interventional study utilized data from Optum's de-identified Clinformatics® Data Mart Database, reflecting events that occurred between January 1, 2011, and December 31, 2019
- Patient inclusion criteria
  - Had ≥2 outpatient claims on separate dates or ≥1 inpatient claim with a schizophrenia diagnosis between January 1, 2012, and June 30, 2019
  - Aged ≥18 years at index (defined as the date of the earliest qualifying schizophrenia diagnosis) (**Figure 1**)
  - Had ≥12 months of continuous pre-index enrollment without a relapse
  - Received ≥1 antipsychotic medication during the 12-month baseline period
- Occurrence and number of relapses and all-cause mortality were evaluated during follow-up
- Relapse was defined as a claim of mental health–related inpatient hospitalization; suicide attempt, self-inflicted harm, or injury (of undetermined intent); homicidal ideation; aggressive or violent behavior; hostility; or incarceration[9]
- A marginal structural model adjusting for baseline (age on the index date, sex, and race) and time-varying (medication use, clinical characteristics) confounding factors was used to estimate hazard ratios (HRs) and 95% CIs

FIGURE 1. Study design



m, month.

TABLE 1. Demographics, baseline characteristics, and relapses during follow-up by relapse group[a]

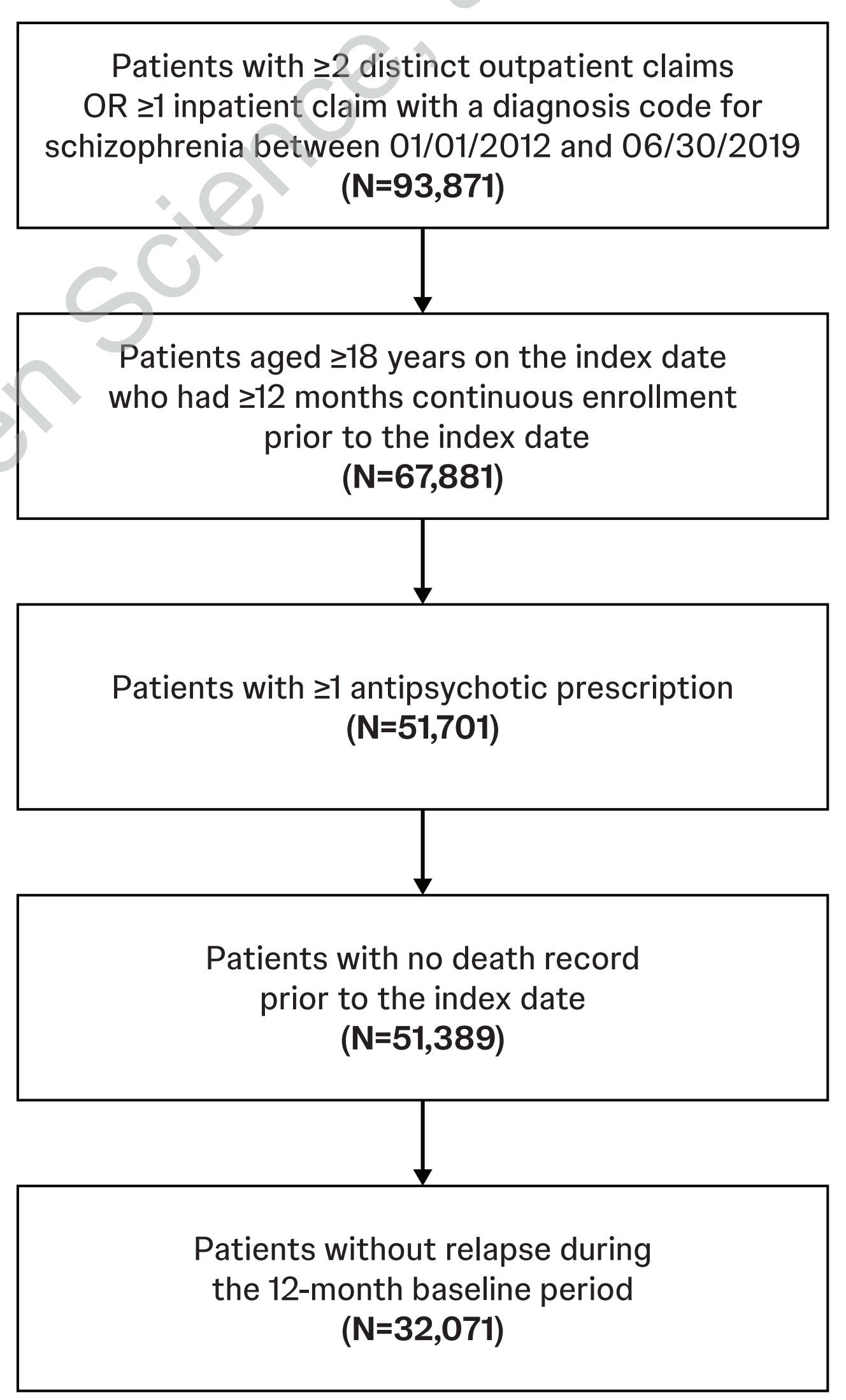
Category	Overall (N=32,071)	No Relapses (n=22,901)	1 Relapse (n=4895)	2 Relapses (n=1833)	3 Relapses (n=926)	4 Relapses (n=548)	5-9 Relapses (n=773)	≥10 Relapses (n=195)	SMD
Age on index date, mean (SD)	57.6 (15.3)	57.0 (15.2)	59.3 (15.5)	59.4 (15.3)	58.9 (15.3)	57.9 (15.2)	57.8 (15.2)	58.7 (16.8)	0.070
Male sex	16,350 (51.0)	11,955 (52.2)	2339 (47.8)	864 (47.1)	438 (47.3)	272 (49.6)	392 (50.7)	90 (46.2)	0.053
Race									
White	17,756 (55.4)	12,440 (54.3)	2741 (56.0)	1100 (60.0)	548 (59.2)	330 (60.2)	485 (62.7)	112 (57.4)	
Black	8233 (25.7)	5930 (25.9)	1242 (25.4)	462 (25.2)	223 (24.1)	151 (27.6)	170 (22.0)	55 (28.2)	**0.113**
Other	6082 (19.0)	4531 (19.8)	912 (18.6)	271 (14.8)	155 (16.7)	67 (12.2)	118 (15.3)	28 (14.4)	
Relapses during follow-up, mean (SD)									
Inpatient relapse	0.38 (1.05)	0	0.61 (0.49)	1.25 (0.81)	1.89 (1.09)	2.38 (1.49)	3.54 (2.29)	5.38 (4.84)	NA
Non-inpatient relapse	0.28 (1.14)	0	0.39 (0.49)	0.75 (0.81)	1.11 (1.09)	1.62 (1.49)	2.69 (2.39)	8.49 (7.48)	NA
Relapse with inpatient stay >30 days	0.05 (0.30)	0	0.08 (0.26)	0.18 (0.45)	0.28 (0.60)	0.35 (0.76)	0.51 (1.05)	0.69 (1.27)	NA
Schizophrenia-related medication use									
First-generation OAP	7187 (22.4)	4863 (21.2)	1193 (24.4)	458 (25.0)	248 (26.8)	148 (27.0)	215 (27.8)	62 (31.8)	0.088
Second-generation OAP	26,513 (82.7)	18,957 (82.8)	4051 (82.8)	1510 (82.4)	754 (81.4)	435 (79.4)	642 (83.1)	164 (84.1)	0.044
First-generation LAI	2214 (6.9)	1451 (6.3)	363 (7.4)	151 (8.2)	100 (10.8)	62 (11.3)	65 (8.4)	22 (11.3)	0.084
Second-generation LAI	2127 (6.6)	1474 (6.4)	303 (6.2)	133 (7.3)	70 (7.6)	58 (10.6)	70 (9.1)	19 (9.7)	0.075
Clozapine	1906 (5.9)	1326 (5.8)	265 (5.4)	126 (6.9)	54 (5.8)	46 (8.4)	67 (8.7)	22 (11.3)	0.092
Lithium	684 (2.1)	453 (2.0)	111 (2.3)	46 (2.5)	33 (3.6)	13 (2.4)	26 (3.4)	–	0.067
Benzodiazepine	2244 (7.0)	1613 (7.0)	358 (7.3)	122 (6.7)	61 (6.6)	30 (5.5)	50 (6.5)	10 (5.1)	0.039
Antidepressant	18,574 (57.9)	13,025 (56.9)	2952 (60.3)	1112 (60.7)	544 (58.7)	341 (62.2)	479 (62.0)	121 (62.1)	0.047
Concomitant medications									
Antidiabetic	8575 (26.7)	5942 (25.9)	1393 (28.5)	529 (28.9)	275 (29.7)	169 (30.8)	212 (27.4)	55 (28.2)	0.042
Antihyperlipidemic	14,355 (44.8)	10,218 (44.6)	2245 (45.9)	808 (44.1)	427 (46.1)	247 (45.1)	333 (43.1)	77 (39.5)	0.051
Antihypertensive	12,385 (38.6)	8716 (38.1)	1966 (40.2)	749 (40.9)	363 (39.2)	215 (39.2)	297 (38.4)	79 (40.5)	0.026
Beta-blocker	8131 (25.4)	5513 (24.1)	1378 (28.2)	523 (28.5)	267 (28.8)	175 (31.9)	223 (28.8)	52 (26.7)	0.061
QCCI, mean (SD)	1.38 (1.82)	1.25 (1.74)	1.67 (1.98)	1.73 (2.03)	1.69 (1.96)	1.76 (2.10)	1.59 (1.82)	1.71 (1.80)	0.093
Mental health–related comorbidities[b]									
Sleep-wake disorders	5200 (16.2)	3608 (15.8)	839 (17.1)	338 (18.4)	168 (18.1)	93 (17.0)	121 (15.7)	33 (16.9)	0.034
Anxiety disorders	8500 (26.5)	5835 (25.5)	1432 (29.3)	503 (27.4)	274 (29.6)	157 (28.6)	236 (30.5)	63 (32.3)	0.058
Neurocognitive disorders	3723 (11.6)	2202 (9.6)	736 (15.0)	327 (17.8)	158 (17.1)	109 (19.9)	140 (18.1)	51 (26.2)	**0.153**
Depressive disorders	10,866 (33.9)	7477 (32.6)	1778 (36.3)	686 (37.4)	349 (37.7)	207 (37.8)	301 (38.9)	68 (34.9)	0.052
Substance related and addictive disorder	7716 (24.1)	5248 (22.9)	1225 (25.0)	530 (28.9)	263 (28.4)	155 (28.3)	246 (31.8)	49 (25.1)	0.081
Other clinical focus areas	5480 (17.1)	3787 (16.5)	869 (17.8)	347 (18.9)	179 (19.3)	103 (18.8)	160 (20.7)	35 (17.9)	0.041
Other comorbidities[b]									
Diabetes	6373 (19.9)	4673 (20.4)	999 (20.4)	333 (18.2)	150 (16.2)	88 (16.1)	111 (14.4)	19 (9.7)	**0.122**
Diabetes without chronic complications	6290 (19.6)	4620 (20.2)	985 (20.1)	327 (17.8)	144 (15.6)	86 (15.7)	109 (14.1)	19 (9.7)	**0.121**
Obesity	4819 (15.0)	3386 (14.8)	733 (15.0)	292 (15.9)	167 (18.0)	89 (16.2)	125 (16.2)	27 (13.8)	0.044
Hypertension	19,049 (59.4)	13,149 (57.4)	3118 (63.7)	1183 (64.5)	607 (65.6)	371 (67.7)	492 (63.6)	129 (66.2)	0.075
Hypertension, uncomplicated	19,048 (59.4)	13,148 (57.4)	3118 (63.7)	1183 (64.5)	607 (65.6)	371 (67.7)	492 (63.6)	129 (66.2)	0.075
Chronic pulmonary disease	3662 (11.4)	2292 (10.0)	667 (13.6)	298 (16.3)	161 (17.4)	81 (14.8)	133 (17.2)	30 (15.4)	0.085
Hypothyroidism	6557 (20.4)	4510 (19.7)	1047 (21.4)	437 (23.8)	217 (23.4)	125 (22.8)	174 (22.5)	47 (24.1)	0.044
Other neurological disorder	5053 (15.8)	3001 (13.1)	1009 (20.6)	452 (24.7)	243 (26.2)	125 (22.8)	180 (23.3)	43 (22.1)	**0.117**
Deficiency anemia	6557 (20.4)	4296 (18.8)	1156 (23.6)	439 (23.9)	255 (27.5)	143 (26.1)	207 (26.8)	61 (31.3)	**0.107**

LAI, long-acting injectable; NA, not available; OAP, oral antipsychotic; QCCI, Quan-Charlson comorbidity index; SMD, standardized mean difference.
[a]Data are n (%) unless otherwise specified. Values for cells that represent fewer than 5 patients are not shown.
[b]Comorbidities occurring in 10% or more of the overall study population.

Results

- The study population included 32,071 patients with relatively stable schizophrenia, defined as no relapse within the 12-month baseline period (**Figure 2**)

FIGURE 2. Patient attrition



Patients with ≥2 distinct outpatient claims OR ≥1 inpatient claim with a diagnosis code for schizophrenia between 01/01/2012 and 06/30/2019 **(N=93,871)**

Patients aged ≥18 years on the index date who had ≥12 months continuous enrollment prior to the index date **(N=67,881)**

Patients with ≥1 antipsychotic prescription **(N=51,701)**

Patients with no death record prior to the index date **(N=51,389)**

Patients without relapse during the 12-month baseline period **(N=32,071)**

Demographics and Baseline Characteristics

- Mean age at index was 57.6 (SD, 15.3) years; the majority of patients (51.0%) were male and 55.4% of patients were White **(Table 1)**
- Most patients (82.7%) had ≥1 prescription for a second-generation OAP, whereas the use of either first- or second-generation LAI antipsychotics was low (<7.0%)
- Mental health–related comorbidities were present in 73.3% of patients
- Common health-related comorbidities not related to mental health included hypertension (59.4%), hypothyroidism (20.4%), and deficiency anemia (20.4%)

Occurrence of Relapse

- During a mean follow-up of 40 months, patients experienced an average of 0.53 (SD, 1.31) relapses
- Of the 9170 patients (28.6%) with a relapse, most experienced 1 episode (53.4%) or 2 episodes (20.0%) (**Table 1**)
- Patients with a lower number of relapses tended to have proportionally more relapses defined by inpatient hospitalizations, whereas those with a higher number of relapses experienced an increase in non-inpatient relapse episodes

Relapse and All-Cause Mortality

- 3974 patients (12.4%) died during the follow-up period
- After adjustment for covariates, the HR for all-cause mortality was significantly higher for patients with 1 relapse versus no relapses (**Table 2**)
- For the first 5 relapses, each subsequent relapse increased all-cause mortality hazard by approximately 20%

TABLE 2. Hazard ratios for mortality by relapse number[a]

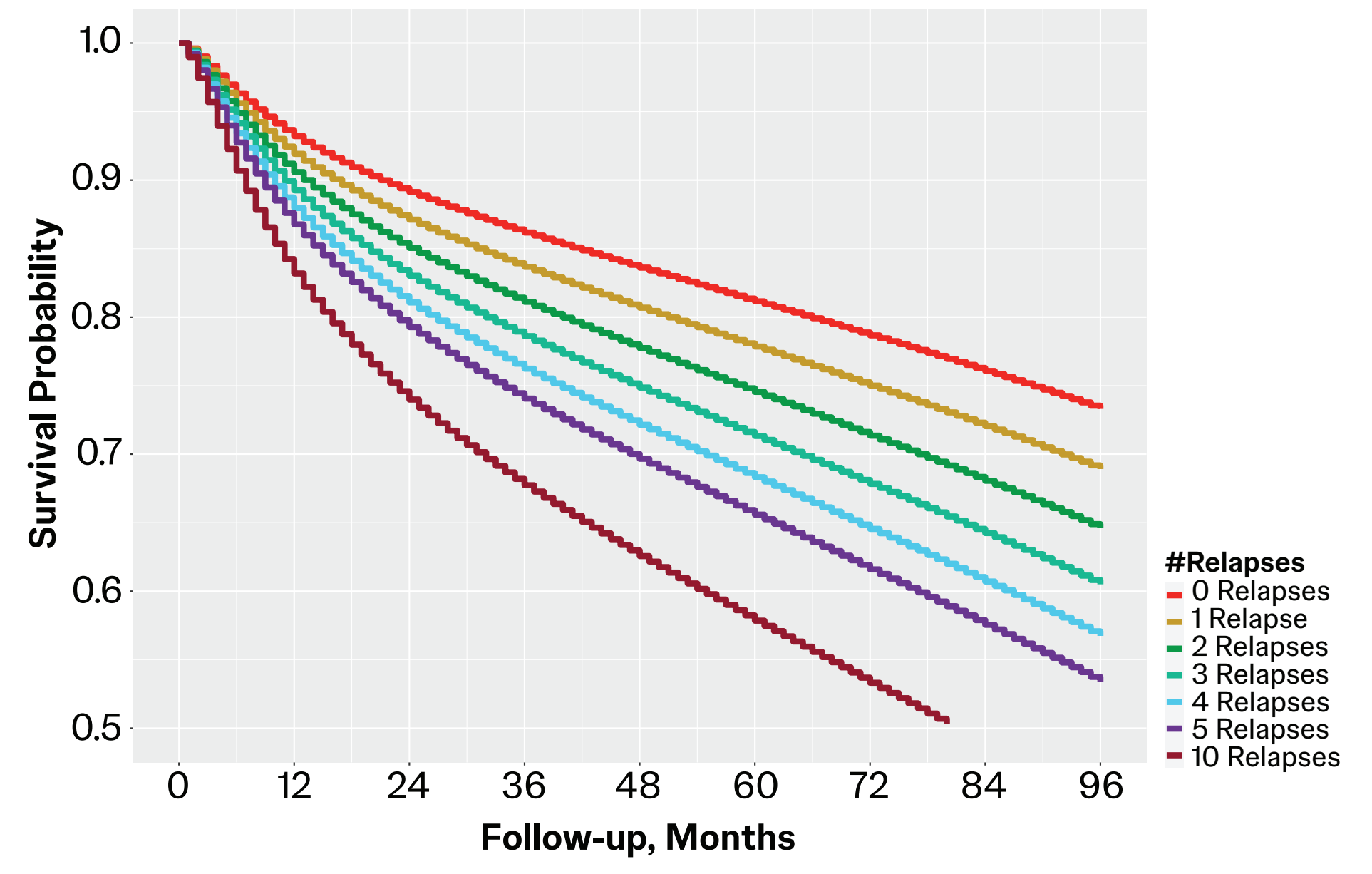
Number of Relapses	Hazard Ratio (95% CI)
No relapses (reference)	1.00
1 relapse	1.20 (1.14–1.26)
2 relapses	1.41 (1.30–1.53)
3 relapses	1.62 (1.45–1.81)
4 relapses	1.83 (1.61–2.07)
5 relapses	2.02 (1.77–2.32)
10 relapses	2.63 (2.02–3.42)

[a]Adjusted for (1) all baseline covariates with a proportion ≥2%, and (2) the time-varying covariates antipsychotic medication use, clozapine, general concomitant medication use, and comorbidities over time.

Predicted Survival

- Estimated 5-year survival was 78% in patients with 1 relapse and only 58% in patients with 10 relapses (**Figure 3**)
- Survival reached 50% within 7 years for patients with 5 relapses

FIGURE 3. Predicted survival curves by relapse number



Key Takeaway

Even a single relapse episode significantly increased all-cause mortality, with each of the first 5 successive relapses amplifying all-cause mortality hazard by an additional 20%

Limitations

- Administrative claims data are limited by the potential for coding errors and inconsistencies, missing clinical or laboratory data, and lack of inclusion of non–clinical factors that influence relapse risk
- Not all indicators of relapse are well represented in claims data, which may lead to undercounting of relapse episodes
- Although multiple sources were used to identify patient deaths, it is possible that not every death was captured in the database, which could lead to outcome misclassification, especially in the form of underreporting
- Results may not be generalizable to all patients with schizophrenia due to regional or national differences in patient demographics, healthcare delivery, and schizophrenia treatment

Conclusions

- ✓ In this study, relapse increased all-cause mortality in patients with relatively stable schizophrenia, and the effect of relapse was cumulative
- ✓ Early interventions that improve healthcare quality and medication adherence may delay relapse and reduce relapse risk, and hence, improve survival in this at-risk population
- ✓ Additional research evaluating cause-specific mortality associated with relapse would be helpful in identifying key preventative strategies

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Disclosures

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