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Excess Mortality and Life-Years Lost in People With Schizophrenia and Other Non-affective Psychoses: An 11-Year Population-Based Cohort Study

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Psychotic disorders are associated with premature mortality, but research was primarily based on Western countries and rarely examined non-affective psychoses other than schizophrenia (ONAP). This population-based cohort study investigated excess mortality in 46 896 schizophrenia and 20 651 ONAP patients between January 2006 and December 2016 in Hong Kong (HK), by estimating all-cause and cause-specific standardized mortality ratios (SMRs), and life-years lost (LYLs), a recently developed, more precise reduced life expectancy measure taking into account the illness onset (age at first-recorded diagnosis). Changes in mortality metrics over the study period were assessed. Study data were retrieved from a territory-wide medical-record database of public healthcare services to 7.5 million HK residents. *Results* showed that schizophrenia and ONAP patients had higher all-cause (schizophrenia: SMR: 2.49 [95% CI: 2.43–2.55]; ONAP: 2.00 [1.92–2.09]), natural-cause (1.80 [1.74–1.85]; 1.47 [1.40–1.54]), and unnatural-cause (6.97 [6.47–7.49]; 8.53 [7.61–9.52]) mortality rates than general population. Respiratory diseases, cardiovascular diseases, and cancers accounted for the majority of deaths in patient cohorts. Men and women with schizophrenia had 9.53 years and 8.07 years of excess LYLs, respectively. For ONAP, excess LYLs was 8.18 years for men and 5.44 years for women. The overall mortality gap remained similar for both patient groups over time despite their improved longevity and declined unnatural-cause mortality rates. Taken together, schizophrenia and ONAP are associated with increased premature mortality and substantially reduced lifespan in a predominantly Chinese population, with excess deaths mainly attributed to a natural cause. Persistent mortality gap highlights an urgent need for targeted interventions to improve the physical health of patients with psychotic disorders.

Key words: schizophrenia/non-affective psychoses/mortality/life years lost/mortality gap/population-based

Introduction

People with schizophrenia and other psychoses exhibit markedly elevated risk of premature mortality,[1,2] with a 10–15 year shorter lifespan relative to the general population.[3] Excess deaths associated with psychotic disorders are mainly attributed to natural causes, particularly cardiovascular disease, respiratory disease, and cancers.[4–7] Evidence shows that such mortality gap has persisted[2,3,8–10] or widened[1,11–13] in recent decades despite the overall increase in life expectancy in the general population due to healthcare improvement. Physical health disparities experienced by people with psychotic disorders thus constitute a serious public health concern that warrants urgent attention. Comprehensive characterization of premature mortality patterns associated with psychotic disorders is critical for policy formulation, resource allocation, and healthcare service optimization to reduce preventable deaths in this vulnerable population.

Of note, existing data on excess mortality in psychotic disorders were primarily derived from Western countries and may not be generalizable to other areas owing to substantial cross-regional variation in healthcare systems, sociocultural context, and population health indices. Thus far, very few studies have been conducted in Asia in this respect and were hampered by important methodological limitations, including small sample size,[14–17] short follow-up duration,[14,17] reliance on data from a single hospital,[15,17] sampling patients with psychiatric inpatient treatment only with a subsequent bias toward greater illness severity,[14,17] and lack of evaluation

for cause-specific mortality[14–20] and change in longevity gap over time.[14–17,19,20] Alternatively, premature mortality in non-affective psychoses other than schizophrenia is rarely studied. Only 2 reports have examined the mortality rate for other non-affective psychoses (ONAP),[21,22] and both revealed that patients with ONAP displayed significantly higher standardized mortality ratio (SMR) than those with schizophrenia. This suggests potential differential mortality risk between schizophrenia and ONAP and awaits further verification. An increasing number of research have assessed the impact of premature mortality on survival in schizophrenia using years of potential life lost (YLLs),[3] which are based on estimated life expectancy at a single fixed age (mostly at birth or 15 y). However, a recent Danish-register study[10,23] that investigated the life expectancy gap between schizophrenia and the general population using life-years lost (LYLs),[24] a measure taking into account different ages of the onset of the disorder,[25] indicated that past estimates of reduced life expectancy are potentially biased and tend to overestimate mortality difference. Until now, there has been no study examining excess LYLs for ONAP.

In this large population-based cohort study, we aimed to comprehensively examine the risk of premature mortality associated with schizophrenia and ONAP over 11 years in Hong Kong (HK), a metropolitan city located at the southeastern tip of China with a population of approximately 7.5 million, utilizing data retrieved from a territory-wide medical-record database of public healthcare services. Specifically, we adopted 2 complementary mortality metrics, namely SMR (for all-cause and cause-specific mortality) and LYLs to quantify the magnitude of excess mortality among patients with schizophrenia and ONAP compared with the general population. Changes in SMRs and excess LYLs across the study period were also assessed to clarify whether the mortality gap improved or worsened over time.

Methods

Data Source

Population statistics and information on all registered deaths in HK between 2006 and 2016 (ie, each calendar year from 2006 to 2016, inclusive) were obtained from the Census and Statistics Department. Data of the patient cohort were extracted from the Clinical Data Analysis and Reporting System (CDARS),[26] a territory-wide electronic health-record database developed by the Hospital Authority (HA), which is a statutory body delivering government-subsidized, universal health coverage to all HK residents (approximately 92% being Chinese) by managing all public hospitals, specialist, and general outpatient clinics in HK. A detailed description of CDARS has been reported elsewhere.[27] Briefly, CDARS is an integrated, longitudinal patient electronic record system capturing clinical data across all healthcare settings of HA facilities.[27] The database contains patients' demographics and clinical information, including diagnoses, attendances to outpatient clinics and emergency departments, and hospital admissions. Data on dates and causes of death were retrieved from CDARS via internal linkage to regional death registries from the Immigration Department. Patients' death status was also directly recorded and verified by CDARS as the vast majority of deaths in HK occur in public hospitals,[28] thereby facilitating accurate ascertainment of death. Clinical data are collected and entered into the computerized clinical management system (CMS) by treating clinicians and other healthcare professionals and are then transferred to CDARS for audit and research purposes. CDARS generates unique, anonymized patient identifiers to protect the privacy and to link all medical records. This database has been used to conduct high-quality population-based studies on various physical and psychiatric conditions,[29,30] including schizophrenia and other psychoses.[31,32]

Study Population and Patient Identification

The study period was between January 1, 2006 and December 31, 2016. We identified all individuals who received a diagnosis of psychotic disorders for public psychiatric inpatient admissions or outpatient care between January 1, 2001 and December 31, 2016 (computerized CMS for psychiatric services implemented since January 1, 2000), and aged ≥18 years during the study period as the study population. Psychotic disorders examined by the study included schizophrenia, schizoaffective disorder, persistent delusional disorder, acute and transient psychotic disorders, and unspecified nonorganic psychosis, with diagnoses being recorded by the International Classification of Diseases, 10th revision (ICD10) code. Patients were categorized into schizophrenia (schizophrenia and schizoaffective disorder: F20 and F25) and other non-affective psychoses (ONAP, psychotic disorders other than "schizophrenia group": F22, F23, F28, and F29) groups for analyses. Diagnostic algorithm was adopted to enhance diagnostic validity. First, the most-recently assigned principal diagnosis of psychotic disorder per patient before the end of follow-up was ascertained as the final diagnosis, which takes into consideration the longitudinal illness course.[33,34] Second, inpatient discharge diagnosis took precedence over outpatient diagnosis in determining patients' final diagnosis. Follow-up of the patient cohort began on the date of the first-recorded final diagnosis of psychotic disorders within the study period. For patients who had been recorded with a diagnosis of psychotic disorders before the study period, their follow-up start date was defined as January 1, 2006. The cohort was followed forward until the date of death or December 31, 2016, whichever came first. The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital

Authority Hong Kong West Cluster. The study data were anonymized and individual patient records were completely unidentifiable during the analysis. Since our study was based on the medical-record database, the requirement for informed consent was waived.

Study Outcomes

Causes of death were classified according to ICD10 codes (supplementary table S1) and were divided into natural and unnatural causes. Natural causes were categorized into infectious and parasitic diseases (A00–B99), neoplasms (C00–D48), cardiovascular diseases (I00–I99), respiratory diseases (J00–J99), digestive diseases (K00–K93), and genitourinary diseases (N00–N99). An array of specific natural causes was also identified for analyses. As data on specific unnatural causes (V01–Y98) were not available, we treated unnatural deaths as a single category for analyses.

Statistical Analysis

SMRs for all-cause and cause-specific deaths and LYLs were calculated as mortality measures. First, the number of observed deaths and person-years of follow-up was computed for each calendar year (2006–2016), sex, and age category (18–24 y, by 5-y age bands from 25 to 84 y, and ≥85 y) for schizophrenia and ONAP groups. The number of person-years for each stratum was multiplied by the respective mortality rate in the general population to produce the expected number of deaths, indirectly standardizing the overall mortality ratio by age, sex, and calendar year. SMRs were estimated by dividing the observed number of deaths by the expected number of deaths. Crude mortality rates (CMRs) per 100 000 person-years as well as SMRs for all-cause and cause-specific deaths of 2 patient groups over the whole study period, stratified by sex and 4 broader age groups (18–34, 35–49, 50–64, and ≥65 y), were then calculated, with 95% confidence intervals (CIs) of SMRs being derived by mid-*P* exact tests. To further illustrate the change in mortality rates with age and how the trends in patients differed from those in the general population, age-specific mortality rates were modeled separately for each group using Poisson regression with cubic splines (supplementary figure S1).

Complete life tables for patient groups were constructed according to the method used in the HK Life Tables to generate life expectancy separately for men and women at each year of age. We computed an average life expectancy at diagnosis (age at first-recorded diagnosis) based on the statistical approach employed by the previous research[10,23,25] to determine excess LYLs for schizophrenia and ONAP patients. This approach takes into account differential numbers at age of diagnosis. Briefly, life expectancy at every single age from 18 years until a set upper limit of 95 years was weighted by the number of patients at that age of diagnosis to derive the average life expectancy at diagnosis. The corresponding measure for the general population (1 set with respect to each of the 2 patient groups, supplementary table S5) was estimated by matching to patient groups on age-specific weightings based on patients' age-of-diagnosis distribution. LYLs denotes the number of years between average life expectancy and 95 years (ie, remaining 95-y restricted life expectancy).[10,23–25] Excess LYLs for men and women in each of the 2 patient groups was calculated as the difference in LYLs between patients and the general population. Thus, excess LYLs refers to the average number of years that patients lose in excess of that observed in the general population of the same sex and age; 95% CIs of excess LYLs were derived from nonparametric bootstrap with 1000 iterations.[23] To investigate the change in mortality gap, we divided the study period into 2 calendar-year periods of 2006–2011 and 2012–2016 and calculated SMRs and excess LYLs of schizophrenia and ONAP patients for these 2 discrete periods for comparison.

Results

The study population included 46 896 schizophrenia patients (men: 22 793 and women: 24 103) with 406 183 person-years of follow-up and 20 651 ONAP patients (men: 7909 and women: 12 742) with 141 664 person-years of follow-up. A total of 6197 deaths in the schizophrenia group and 2191 deaths in the ONAP group were observed, of which 4966 (80.1%) and 1849 (84.4%) had a known cause, respectively. The numbers of person-years and cause-specific death counts for each demographic subgroup of 2 patient groups are listed in supplementary table S2. The numbers of all-cause, natural-cause, unnatural-cause, and unknown-cause death counts for each demographic subgroup of 2 patient groups for 2 calendar-year periods are summarized in supplementary table S3.

All-Cause Mortality Rates

All-cause SMRs for schizophrenia and ONAP were significantly increased in the total sample (schizophrenia: SMR 2.49 [95% CI 2.43–2.55]; ONAP: 2.00 [1.92–2.09]) and in each demographic subgroup relative to the general population (tables 1–3, supplementary table S4 and supplementary figure S1). All-cause SMRs were higher for men than for women, and decreased with age, with particularly high SMR in the youngest age group (schizophrenia: 11.68 [10.37–13.11]; ONAP: 12.60 [10.73–14.71]). Schizophrenia patients had higher all-cause SMRs than ONAP patients in both sexes, and across age groups except among patients aged 18–34 years.

Natural-Cause and Unnatural-Cause Mortality Rates

In both patient groups, SMRs for natural and unnatural causes were significantly increased in the total sample and in each demographic subgroup (tables 1–3,

Table 1. Observed Deaths, Crude Mortality Rates, and All-Cause and Cause-Specific Standardized Mortality Ratios of Patients With Schizophrenia and Other Non-affective Psychoses

	Schizophrenia			Other Non-affective Psychoses		
Cause of death	Deaths	CMR[a]	SMR (95% CI)	Deaths	CMR	SMR (95% CI)
All causes	6197	1525.7	2.49 (2.43–2.55)	2191	1546.6	2.00 (1.92–2.09)
Natural causes	4250	1046.3	1.80 (1.74–1.85)	1542	1088.4	1.47 (1.40–1.54)
Cardiovascular diseases	808	198.9	1.38 (1.29–1.48)	279	196.9	1.03 (0.89–1.13)
Ischemic heart disease	367	90.4	1.51 (1.36–1.67)	131	92.5	1.21 (1.02–1.43)
Non-ischemic heart diseases	187	46.0	1.70 (1.47–1.96)	71	50.1	1.29 (1.01–1.62)
Cerebrovascular diseases	214	52.7	1.14 (0.99–1.30)	72	50.8	0.82 (0.64–1.02)
Neoplasms	878	216.2	0.97 (0.91–1.03)	284	200.5	0.87 (0.77–0.98)
Lung cancer	191	47.0	0.77 (0.67–0.89)	48	33.9	0.55 (0.41–0.72)
Liver cancer	118	29.1	1.10 (0.91–1.31)	35	24.7	1.05 (0.74–1.44)
Colon cancer	91	22.4	1.10 (0.89–1.35)	27	19.1	0.83 (0.56–1.19)
Breast cancer	60	14.8	1.29 (0.99–1.65)	25	17.6	1.39 (0.92–2.03)
Respiratory diseases	1642	404.3	3.82 (3.64–4.01)	637	449.7	2.68 (2.48–2.90)
Non-aspiration pneumonia	1390	342.2	4.60 (4.37–4.85)	538	379.8	3.07 (2.82–3.34)
Aspiration pneumonia	85	20.9	6.53 (5.25–8.04)	21	14.8	2.85 (1.81–4.28)
Chronic obstructive pulmonary disease	49	12.1	0.64 (0.48–0.84)	31	21.9	0.83 (0.57–1.16)
Digestive diseases	210	51.7	2.35 (2.05–2.69)	71	50.1	1.84 (1.45–2.31)
Liver diseases	57	14.0	1.73 (1.32–2.22)	19	13.4	1.72 (1.07–2.64)
Pancreaticobiliary diseases	30	7.4	2.17 (1.49–3.05)	17	12.0	2.27 (1.36–3.55)
Genitourinary diseases	239	58.8	2.07 (1.82–2.34)	92	64.9	1.62 (1.31–1.97)
Renal failure	165	40.6	1.93 (1.65–2.24)	58	40.9	1.44 (1.10–1.85)
Infectious and parasitic diseases	185	45.5	2.83 (2.44–3.26)	72	50.8	2.35 (1.85–2.94)
Unnatural causes	716	176.3	6.97 (6.47–7.49)	307	216.7	8.53 (7.61–9.52)

Note: CI, confidence interval; CMR, crude mortality rate; SMR, standardized mortality ratio (standardized for age, sex, and calendar year).
[a]CMRs are presented as the numbers of deaths per 100 000 person-years.

supplementary table S4 and supplementary figure S1). Natural-cause SMRs were higher for schizophrenia (1.80 [1.74–1.85]) than for ONAP (1.47 [1.40–1.54]), for men than for women, and generally decreased with age. In contrast, unnatural-cause SMRs were higher for ONAP (8.53 [7.61–9.52]) than for schizophrenia (6.97 [6.47–7.49]), and decreased with age, with markedly elevated SMR in the youngest age group (schizophrenia: 16.65 [14.30–19.27]; ONAP: 19.27 [15.77–23.31]).

Distributions of causes of death were similar between 2 patient groups, with natural causes accounting for most of the known-cause deaths. Approximately, two-thirds of all known-cause deaths were attributed to respiratory diseases, cancers, and cardiovascular diseases (table 1). Respiratory diseases represented the leading cause of death and accounted for around one-third of all known-cause deaths. Cancers and cardiovascular diseases each contributed to about 1 in 6 known-cause deaths, with nearly half of the cardiovascular-related deaths being due to ischemic heart disease. Unnatural causes accounted for approximately 1 in 7 and 1 in 6 known-cause deaths in schizophrenia and ONAP groups, respectively. In both patient groups, men had generally higher CMRs for most listed causes of death than women (table 2). The mortality rate for most natural causes increased with age while that for unnatural causes decreased with age (table 3, supplementary table S4).

Schizophrenia patients had higher SMRs for all broad categories of natural causes than ONAP patients (table 1). Respiratory diseases displayed the highest SMR among natural-cause categories in schizophrenia (3.82 [3.64–4.01]) and ONAP (2.68 [2.48–2.90]), with pneumonia (non-aspiration and aspiration) showing the highest SMRs across all listed specific natural causes, particularly among men and age groups <65 years (tables 1–3, supplementary table S4). Conversely, SMR for chronic obstructive pulmonary disease (COPD) was lower in schizophrenia and not elevated in ONAP (albeit with increased SMR in both patient groups aged 50–64 y). The SMR for cardiovascular diseases was significantly elevated in schizophrenia (1.38 [1.29–1.48]) but not in ONAP (1.03 [0.89–1.13]). In both patient groups, SMRs were significantly increased for ischemic heart disease, but not for cerebrovascular disease except among schizophrenia patients aged 50–64 years (tables 1–3, supplementary table S4). The SMRs for digestive diseases, genitourinary diseases, and infectious and parasitic diseases were all significantly elevated in schizophrenia (ranged: 2.07–2.83) and ONAP (ranged: 1.62–2.35) (table 1). Neither schizophrenia nor ONAP was associated with increased mortality rates from cancers compared with the general population, and SMR for lung cancer was lower in both patient groups.

Table 2. Crude Mortality Rates and All-Cause and Cause-Specific Standardized Mortality Ratios of Patients With Schizophrenia and Other Non-affective Psychoses by Sex

	Schizophrenia				Other Non-affective Psychoses			
	Men		Women		Men		Women	
Cause of death	CMR[a]	SMR (95% CI)	CMR	SMR (95% CI)	CMR	SMR (95% CI)	CMR	SMR (95% CI)
All causes	1724.5	2.58 (2.50–2.67)	1335.4	2.39 (2.30–2.48)	1946.4	2.20 (2.07–2.33)	1300.4	1.85 (1.75–1.96)
Natural causes	1179.2	1.88 (1.81–1.96)	919.2	1.71 (1.63–1.78)	1322.2	1.57 (1.46–1.69)	944.5	1.39 (1.30–1.48)
Cardiovascular diseases	202.9	1.36 (1.23–1.50)	195.1	1.41 (1.28–1.55)	235.2	1.16 (0.97–1.38)	173.4	0.95 (0.81–1.11)
Ischemic heart disease	99.7	1.44 (1.25–1.65)	81.4	1.61 (1.38–1.87)	127.8	1.42 (1.11–1.78)	70.7	1.05 (0.81–1.33)
Non-ischemic heart diseases	39.3	1.70 (1.35–2.11)	52.5	1.70 (1.40–2.04)	48.1	1.42 (0.95–2.06)	51.3	1.22 (0.90–1.62)
Cerebrovascular diseases	53.9	1.19 (0.98–1.43)	51.5	1.09 (0.90–1.31)	66.7	1.04 (0.74–1.43)	41.1	0.67 (0.48–0.92)
Neoplasms	226.6	0.88 (0.80–0.96)	206.2	1.08 (0.98–1.19)	214.8	0.76 (0.63–0.90)	191.6	0.97 (0.83–1.13)
Lung cancer	68.5	0.87 (0.73–1.03)	26.5	0.60 (0.46–0.78)	51.9	0.59 (0.40–0.85)	22.8	0.50 (0.31–0.75)
Liver cancer	40.8	1.04 (0.83–1.28)	17.8	1.26 (0.90–1.72)	44.4	1.18 (0.77–1.72)	12.5	0.85 (0.45–1.47)
Colon cancer	19.6	0.93 (0.67–1.25)	25.1	1.29 (0.97–1.67)	14.8	0.58 (0.27–1.09)	21.7	1.01 (0.63–1.55)
Breast cancer	0	0	28.9	1.30 (1.00–1.66)	0	0	28.5	1.40 (0.92–2.03)
Respiratory diseases	489.4	4.18 (3.92–4.45)	322.8	3.39 (3.14–3.66)	577.8	2.81 (2.51–3.13)	370.7	2.58 (2.31–2.87)
Non-aspiration pneumonia	418.9	5.61 (5.24–6.00)	268.8	3.63 (3.34–3.94)	477.8	3.47 (3.06–3.91)	319.4	2.78 (2.47–3.12)
Aspiration pneumonia	23.2	7.73 (5.72–10.22)	18.8	5.52 (3.98–7.48)	24.1	4.60 (2.56–7.67)	9.1	1.76 (0.82–3.34)
Chronic obstructive pulmonary disease	17.6	0.60 (0.42–0.82)	6.7	0.79 (0.45–1.29)	38.9	0.79 (0.50–1.19)	11.4	0.93 (0.47–1.65)
Digestive diseases	68.0	2.79 (2.35–3.29)	36.1	1.83 (1.45–2.28)	57.4	1.87 (1.29–2.62)	45.6	1.82 (1.32–2.45)
Liver diseases	19.6	1.82 (1.31–2.46)	8.7	1.56 (0.95–2.42)	20.4	1.93 (1.01–3.35)	9.1	1.51 (0.70–2.86)
Pancreaticobiliary diseases	7.6	2.53 (1.47–4.09)	7.2	1.89 (1.10–3.05)	9.3	1.86 (0.68–4.13)	13.7	2.49 (1.35–4.23)
Genitourinary diseases	51.4	2.11 (1.73–2.56)	66.0	2.04 (1.72–2.40)	74.1	2.00 (1.45–2.70)	59.3	1.41 (1.06–1.83)
Renal failure	38.3	2.01 (1.59–2.50)	42.9	1.87 (1.51–2.29)	51.9	1.86 (1.26–2.66)	34.2	1.19 (0.82–1.68)
Infectious and parasitic diseases	54.9	3.14 (2.59–3.77)	36.6	2.48 (1.97–3.09)	63.0	2.56 (1.80–3.54)	43.3	2.19 (1.57–2.97)
Unnatural causes	199.9	6.00 (5.43–6.61)	153.7	8.71 (7.79–9.70)	309.3	8.56 (7.33–9.93)	159.7	8.49 (7.17–9.99)

Note: CI, confidence interval; CMR, crude mortality rate; SMR, standardized mortality ratio (standardized for age, sex, and calendar year).
[a]CMRs are presented as the numbers of deaths per 100 000 person-years.

Table 3. Crude Mortality Rates and All-Cause and Cause-Specific Standardized Mortality Ratios of Patients With Schizophrenia by Age Group

	18–34 Years		35–49 Years		50–64 Years		≥65 Years	
	CMR[a]	SMR (95% CI)	CMR	SMR (95% CI)	CMR	SMR (95% CI)	CMR	SMR (95% CI)
All causes	498.3	11.68 (10.37–13.11)	518.6	4.48 (4.16–4.81)	1244.6	3.10 (2.96–3.25)	5221.4	1.97 (1.91–2.04)
Natural causes	65.8	3.11 (2.22–4.24)	217.2	2.32 (2.07–2.59)	869.7	2.32 (2.20–2.46)	4085.4	1.58 (1.52–1.64)
Cardiovascular diseases	7.1	1.66 (0.53–3.99)	43.6	2.07 (1.60–2.64)	172.0	2.31 (2.04–2.62)	761.9	1.12 (1.02–1.22)
Ischemic heart disease	0	0	19.7	2.16 (1.46–3.07)	78.6	2.30 (1.90–2.76)	348.0	1.26 (1.10–1.43)
Non-ischemic heart diseases	5.3	3.42 (0.87–9.31)	12.6	3.34 (2.04–5.17)	43.5	3.71 (2.87–4.73)	159.4	1.19 (0.98–1.44)
Cerebrovascular diseases	1.8	1.48 (0.07–7.30)	8.4	1.31 (0.71–2.23)	44.9	1.98 (1.54–2.51)	21.0	0.94 (0.79–1.10)
Neoplasms	8.9	0.94 (0.34–2.08)	64.7	1.23 (1.00–1.50)	233.0	1.06 (0.95–1.18)	688.3	0.87 (0.79–0.95)
Lung cancer	0	0	9.1	0.95 (0.53–1.58)	49.8	0.89 (0.70–1.12)	164.0	0.70 (0.57–0.84)
Liver cancer	3.6	2.86 (0.48–9.46)	9.1	1.33 (0.74–2.22)	31.6	1.06 (0.78–1.41)	88.9	1.06 (0.81–1.36)
Colon cancer	0	0	4.2	1.28 (0.52–2.67)	16.8	1.01 (0.67–1.49)	93.5	1.13 (0.87–1.44)
Breast cancer	0	0	4.2	0.76 (0.31–1.57)	21.1	1.29 (0.89–1.82)	36.8	1.60 (1.05–2.34)
Respiratory diseases	28.5	13.68 (8.10–21.74)	47.8	9.35 (7.32–11.78)	234.5	8.28 (7.43–9.20)	1876.4	3.21 (3.03–3.39)
Non-aspiration pneumonia	24.9	18.03 (10.27–29.54)	39.4	11.76 (8.97–15.16)	184.6	10.37 (9.17–11.68)	1620.4	3.90 (3.67–4.14)
Aspiration pneumonia	1.8	12.64 (0.63–62.34)	1.4	7.05 (1.18–23.28)	20.4	23.45 (16.00–33.24)	81.2	4.64 (3.51–6.03)
COPD	0	0	0.7	2.76 (0.14–13.59)	9.8	2.19 (1.25–3.59)	52.1	0.49 (0.34–0.67)
Digestive diseases	1.8	2.77 (0.14–13.66)	14.1	3.81 (2.39–5.78)	65.3	4.50 (3.66–5.49)	147.2	1.52 (1.24–1.85)
Liver diseases	0	0	6.3	2.84 (1.39–5.22)	20.4	2.48 (1.69–3.51)	29.1	1.06 (0.65–1.62)
Pancreaticobiliary diseases	1.8	21.06 (1.05–103.85)	1.4	4.65 (0.78–15.36)	6.3	6.47 (3.16–11.88)	27.6	1.50 (0.92–2.33)
Genitourinary diseases	1.8	4.41 (0.22–21.77)	9.1	4.72 (2.630–7.87)	49.8	4.79 (3.77–6.00)	236.1	1.58 (1.34–1.84)
Renal failure	1.8	5.17 (0.26–25.51)	7.7	5.00 (2.63–8.70)	40.0	4.75 (3.63–6.11)	147.2	1.35 (1.10–1.64)
Infectious and parasitic diseases	1.8	1.86 (0.09–9.16)	10.5	3.82 (2.22–6.16)	36.5	4.23 (3.19–5.50)	179.4	2.41 (2.00–2.87)
Unnatural causes	307.9	16.65 (14.30–19.27)	181.3	9.82 (8.67–11.07)	139.0	6.43 (5.58–7.38)	133.4	2.46 (1.98–3.02)

Note: CI, confidence interval; CMR, crude mortality rate; COPD, chronic obstructive pulmonary disease, SMR, standardized mortality ratio (standardized for age, sex, and calendar year).

[a]CMRs are presented as the numbers of deaths per 100 000 person-years.

Excess LYLs and Change in Mortality Gap Over Time

As shown in table 4, schizophrenia patients had more excess LYLs than ONAP patients in both sexes. Men and women with schizophrenia had 9.53 and 8.07 excess LYLs, respectively, compared with the general population of the same age. In the ONAP group, excess LYLs was 8.19 years for men and 5.44 years for women.

All-cause SMR was reduced for ONAP (2.03 vs 1.72) but showed minimal change for schizophrenia (2.52 vs 2.47) across 2 calendar-year periods (2006–2011 and 2012–2016). Both patient groups exhibited markedly reduced unnatural-cause SMRs, particularly among women. However, natural-cause SMRs were similar across 2 periods for schizophrenia and ONAP (table 5). Excess LYLs was lessened for ONAP, especially in women

Table 4. Life-Years Lost and Excess Life-Years Lost in Patients With Schizophrenia and Other Non-affective Psychoses

	Schizophrenia		Other Non-affective psychoses	
	Life-years lost[a]	Excess LYLs[b] (95% CI)	Life-years lost	Excess LYLs (95% CI)
The whole study period				
Men	23.01	9.53 (9.11–9.93)	21.04	8.19 (7.47–8.94)
Women	16.02	8.07 (7.70–8.46)	13.10	5.44 (4.81–6.00)
By calendar period				
Men				
2006–2011	23.12	9.03 (8.47–9.60)	21.81	8.37 (7.17–9.44)
2012–2016	22.77	9.91 (9.31–10.44)	20.51	8.25 (7.32–9.09)
Women				
2006–2011	16.10	7.71 (7.15–8.27)	14.60	6.52 (5.57–7.46)
2012–2016	15.87	8.37 (7.85–9.93)	11.82	4.60 (3.86–5.40)

Note: CI, confidence interval; LYLs, life-years lost.
[a]Life-years lost denotes the difference between the average life expectancy of the study population at age of diagnosis and the set reference age (95 years).
[b]Excess life-years lost denotes the difference in LYLs between the study population and the general population.

Table 5. Standardized Mortality Ratios of Patients With Schizophrenia and Other Non-affective Psychoses for All Causes, Natural Causes, and Unnatural Causes by Sex, Age, and Calendar Period

	SMR (95% CI)					
	All Causes		Natural Causes		Unnatural Causes	
	2006–2011	2012–2016	2006–2011	2012–2016	2006–2011	2012–2016
			Schizophrenia			
Total	2.52 (2.43–2.61)	2.47 (2.38–2.56)	1.82 (1.74–1.90)	1.78 (1.70–1.85)	8.02 (7.31– 8.79)	5.66 (5.01–6.38)
Sex						
Men	2.58 (2.46–2.71)	2.58 (2.46–2.71)	1.90 (1.79–2.01)	1.86 (1.76–1.97)	6.63 (5.83– 7.50)	5.21 (4.44–6.09)
Women	2.44 (2.31–2.57)	2.34 (2.22–2.47)	1.73 (1.62–1.84)	1.68 (1.58–1.79)	10.61 (9.25–12.12)	6.45 (5.31–7.75)
Age (y)						
18–34	11.79 (10.16–13.61)	11.49 (9.39–13.91)	2.20 (1.30–3.49)	4.56 (2.90– 6.86)	17.85 (14.93–21.18)	14.10 (10.48–18.59)
35–49	4.73 (4.30–5.19)	4.16 (3.71–4.65)	2.60 (2.25–2.99)	1.98 (1.65– 2.37)	10.21 (8.72–11.88)	9.22 (7.52–11.20)
50–64	3.13 (2.93–3.34)	3.07 (2.88–3.28)	2.37 (2.19–2.56)	2.27 (2.10–2.46)	7.14 (5.94–8.52)	5.61 (4.48–6.95)
≥65	1.90 (1.81–1.99)	2.04 (1.95–2.14)	1.57 (1.48–1.66)	1.59 (1.51–1.68)	2.88 (2.16–3.77)	2.06 (1.47–2.81)
			Other Non-Affective Psychoses			
Total	2.03 (1.91–2.16)	1.72 (1.62–1.82)	1.48 (1.37–1.59)	1.46 (1.36–1.56)	10.22 (8.80–11.81)	6.96 (5.84–8.23)
Sex						
Men	2.16 (1.97–2.36)	1.94 (1.79–2.11)	1.52 (1.36–1.70)	1.61 (1.46–1.78)	9.59 (7.76–11.71)	7.59 (6.02–9.44)
Women	1.93 (1.77–2.10)	1.55 (1.43–1.68)	1.44 (1.30–1.59)	1.35 (1.23–1.48)	10.99 (8.85–13.51)	6.23 (4.73–8.07)
Age (y)						
18–34	14.05 (11.43–17.10)	7.89 (6.08–10.09)	3.95 (2.14–6.72)	2.55 (1.18–4.84)	20.42 (15.76–26.05)	17.74 (12.84–23.92)
35–49	5.15 (4.26–6.18)	3.53 (2.87–4.30)	1.77 (1.21–2.49)	1.96 (1.42–2.64)	16.14 (12.40–20.68)	10.53 (7.56–14.31)
50–64	2.94 (2.52–3.41)	2.24 (1.95–2.58)	2.15 (1.77–2.58)	1.77 (1.49–2.10)	11.69 (8.35–15.94)	9.14 (6.50–12.52)
≥65	1.56 (1.44–1.68)	1.46 (1.37–1.57)	1.36 (1.25–1.48)	1.38 (1.28–1.49)	2.66 (1.67–4.04)	1.80 (1.07–2.86)

Note: CI, confidence interval; SMR, standardized mortality ratio (standardized for age, sex, and calendar year).

(−1.92 y; significantly reduced over time as indicated by nonoverlapping 95% CIs), but was slightly increased for schizophrenia (men: +0.88 y and women: +0.66 y) (table 4). There was a decrease in LYLs (increased life expectancy) in both patient groups over time, albeit more pronounced for ONAP.

Discussion

To our knowledge, this is the first Asian study using LYLs complementary with relative mortality risk measure (SMR) to evaluate the excess mortality associated with schizophrenia. This is also one of the very few studies[10,23] which examined reduced life expectancy by estimating excess LYLs for schizophrenia and the first for ONAP in this respect. Our results showed that patients with schizophrenia and ONAP had 2.5- and 2-fold increased mortality risk compared with the general population, respectively. Both patient groups were associated with a substantially shorter lifespan than the general population, particularly men, with on average 8–9 years more LYLs for schizophrenia and 5–8 years more LYLs for ONAP. Natural causes, specifically respiratory diseases, cardiovascular diseases, and cancers, accounted for the majority of known-cause deaths, while unnatural causes had markedly elevated SMR, especially among patients aged <35 years. The mortality gap remained similar over 11 years for both groups, except slight improvement in women with ONAP.

Our finding on all-cause SMR for schizophrenia is broadly consistent with the literature which reported 2–3 times greater overall mortality risk than the general population[2] and is similar to some of the recent studies[9,20,35] as well as an earlier meta-analysis[1] showing median all-cause SMR of 2.58 for schizophrenia. Notably, although we affirmed that schizophrenia was associated with considerably shortened remaining life expectancy after diagnosis, our observed magnitude of longevity gap is smaller than most previous estimates based on YLLs, with a recent meta-analysis revealing that schizophrenia patients had 14.5 years shorter in lifespan than the general population.[3] Recent research, however, suggests that LYLs method yields more precise, albeit more conservative, estimates than prior measures of reduced life expectancy by incorporating variations in age of the onset of the disorder into life expectancy calculation.[10,23,25] This also accords with the results of a Taiwan study demonstrating that the expected life expectancy for schizophrenia patients decreased significantly with increasing age at diagnosis.[19]

In line with previous studies,[1,4–7] we found that cardiovascular diseases, respiratory diseases, and cancers represented the major contributors to natural-cause deaths for schizophrenia and ONAP. Substantial evidence has shown that schizophrenia is associated with an increased incidence of cardiovascular diseases[36] and elevated mortality rate following acute coronary syndrome even when inequitable cardiac care was taken into consideration.[32,37] Lifestyle modification as well as early detection and optimal treatment of comorbid diabetes, dyslipidemia, and hypertension should be implemented to reduce cardiovascular-related mortality in schizophrenia. Our results that respiratory diseases displayed the highest CMR and SMR across all natural-cause categories concur with past studies indicating respiratory diseases as one of the leading causes of death for schizophrenia with a high relative mortality rate.[5–7,10,23] A recent study further revealed that respiratory diseases exerted the largest contribution, as measured by population attributable fraction (PAF), to the overall mortality in schizophrenia among other physical disease categories.[7] Non-aspiration pneumonia accounted for the majority of our observed respiratory-related deaths for schizophrenia and ONAP. This generally aligns with accumulating evidence showing that schizophrenia patients have a higher risk of pneumonia[38] and worse post-pneumonia outcomes including increased mortality[39] than the general population. However, we noted that the proportion of respiratory-related deaths attributed to COPD was small and schizophrenia patients had lower COPD mortality rate than the general population. This is contrary to most previous studies demonstrating elevated COPD mortality risk in schizophrenia.[4,5] One possible explanation is that a significant proportion of our patients with pneumonia as their assigned cause of death might have underlying COPD, a risk factor of and one of the most frequent comorbidities with pneumonia, which is a major cause of death among COPD patients.[40] As our mortality analysis was based on a single cause of death per deceased person, this may introduce inaccuracy in death-cause assignment for patients with multi-comorbidity, which is nonetheless more common in schizophrenia patients than the general population. Alternatively, our findings that mortality rates for cancers were not significantly elevated among patient groups are at odds with most,[41] though not all,[42] past studies reporting heightened cancer mortality rate in schizophrenia. However, our cancer-specific SMRs might be underestimated owing to the missing data on patients' cause of death (19.9% for schizophrenia and 15.6% for ONAP) and potential misclassification bias in cause-of-death ascertainment. Non-elevated cancer-specific SMRs might also be attributable to a markedly reduced lifespan in patients with psychotic disorders, rendering them more likely to die from non-cancer causes, especially among the elderly age group. This echoes with recent findings that schizophrenia patients lost fewer years of life related to cancers than the general population.[10,23]

Patients with schizophrenia and ONAP had 7–8 times greater risk of dying from unnatural causes than the general population. Such mortality rate was particularly elevated among the youngest age group, with up to

16- to 19-fold increased risk for unnatural-cause deaths. Of note, our lack of information regarding specific unnatural causes precludes us from clarifying the mortality risk of suicide, which has been consistently shown to predominate unnatural deaths for psychotic disorders. That said, our results are concordant with prior studies indicating that suicide risk is highest during the initial few years following first-episode psychosis,[43] which typically emerges in late adolescence and early adulthood. This underscores a pivotal role of early intervention services on lowering suicide risk among people presenting with first-episode psychosis.[44]

Our results indicated that schizophrenia patients exhibited slightly greater overall SMR and shorter remaining life expectancy after diagnosis than ONAP patients. This is opposed to the findings of 2 other studies, which also examined premature mortality for schizophrenia and ONAP separately but revealed that the former had lower all-cause SMR than the latter.[21,22] Conversely, we noted that unnatural-cause mortality rate was higher for ONAP than for schizophrenia across all age groups except those ≥65 years. Discrepancies might partly be attributable to methodological variations. In particular, these 2 earlier studies[21,22] identified patients with ONAP using ICD9 criteria, which included a diagnostic category of "psychoses with origin specific to childhood," comprising conditions that are pervasive developmental disorders rather than psychotic disorder per se. Owing to the paucity of existing data, further investigation is required to clarify potential differential patterns of excess mortality between schizophrenia and ONAP.

The overall mortality gap for schizophrenia and ONAP remained largely unchanged over 11 years. Despite the reduction in unnatural-cause SMRs across the study period, natural-cause mortality difference was unimproved over time. Moreover, although life expectancy increased across all groups, the magnitude of improved longevity was smaller in schizophrenia patients compared with the general population. Our findings thus agree with many studies showing either constant[2,3,8–10] or even widened[1,11–13] mortality gap associated with schizophrenia. This indicates that physical health disparities persist and the benefits of improved medical care on increased lifespan in the general population are not equally shared by patients with psychotic disorders.

Several study limitations should be noted. First, a number of premature mortality risk factors such as unhealthy lifestyles and obesity were not adequately recorded in the medical database and thus were not included in the analysis. Second, missing data on patients' death causes may compromise the accuracy in evaluating cause-specific SMRs and potential change in mortality gap over time and preclude us from generating reliable estimates of cause-specific LYLs using a decomposition model as applied by prior studies.[10,23] Third, as information on specific unnatural causes was not available, we were not able to investigate mortality risk for individual categories of unnatural deaths including suicide and accidents. Fourth, a proportion of patients may have the first-recorded diagnosis before the study period. This would result in survival bias (ie, patients with the highest risk of death may have died prior to study follow-up) which may contribute to our results of reduced mortality rates with age and may affect our estimation of change in mortality rates over time in patient cohorts. Fifth, patients' age of illness onset was defined by age of the first-recorded diagnosis which may overestimate the actual age of onset of psychotic disorders, and hence the LYLs may be underestimated. Sixth, patients' data were retrieved from the medical-record database of public healthcare services managed by HA, and patients who were under private psychiatric care were not included in the study. However, the HA is the predominant provider of psychiatric services to individuals with severe mental disorders (especially psychotic disorders) in HK, and hence the risk of selection bias or missing treated cases of psychotic disorders was minimized. Seventh, CDARS-derived diagnoses of psychotic disorders have not been systematically validated. We have employed a diagnostic algorithm to minimize diagnostic misclassification, and evidence has shown that the clinical diagnosis of psychotic disorders routinely collected in the health-record database is generally reliable for research.[45] Nonetheless, future study evaluating the validity of CDARS-derived diagnoses would facilitate the estimation of potential impact of misdiagnosis bias on outcome analyses. Lastly, as HK is a highly urbanized, densely populated city and is categorized by the World Bank as a high-income economy,[46] our findings may not be generalizable to mainland China or other Asian regions.

In conclusion, this large population-based study indicates that schizophrenia and ONAP patients have heightened mortality risk and markedly reduced life expectancy in a predominantly Chinese population, with excess mortality being primarily due to natural causes. Our findings that such differential mortality gap remained similar across the study period highlights an urgent need for targeted interventions to promote the physical health of patients with psychotic disorders so as to significantly reduce their risk of preventable physical morbidity and premature mortality.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin*.

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