Risk of All-Cause and Suicide Death in Patients With Schizophrenia:

An Entire-Population Longitudinal Study in Taiwan

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Abstract

Background: Schizophrenia increases mortality from all causes and specific causes. Comprehensive research on modifiable risk factors for early mortality from multiple sources is needed.

Methods: Taiwan's National Health Insurance Research Database, which contains claims data from a lifetime insurance program for the whole population, provided extensive medical inpatient and outpatient data categorized by *ICD-9-CM* and *ICD-10* for this nationwide retrospective longitudinal cohort study. The National Mortality Registry provided data on all-cause, natural, suicide, and accidental deaths. 191,553 patients with schizophrenia and 26,362,448 individuals without schizophrenia were monitored from January 1, 2003, to December 31, 2017. Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for mortality risk were calculated using Cox regression models. We compared different mortality risks associated with schizophrenia across age, sex, and Charlson Comorbidity Index (CCI) subgroups.

Results: We found that schizophrenia results in a relatively higher increase in suicidal mortality in those aged ≤ 20 years (aHR = 15.55; 95% CI, 13.95–17.34), and that effect decreased with age. The effect of schizophrenia in female individuals (suicide death: female, aHR = 11.82, 95% CI, 11.21–12.46; male, aHR = 8.11, 95% CI, 7.77–8.47; difference, $P < .001$) and individuals without comorbidity (natural cause of death, CCI = 0 aHR = 5.94, 95% CI, 5.68–6.22; CCI = 1–2 aHR = 3.62, 95% CI, 3.52–3.73; CCI > 2 aHR = 1.61, 95% CI, 1.58–1.64) led to comparatively higher mortality risks. The effect of schizophrenia in individuals with AIDS (suicide death, aHR = 2.73, 95% CI, 1.70–4.39) resulted in a relatively smaller increase in suicide mortality compared to individuals with other comorbidities; however, in patients with connective tissue diseases, a diagnosis of schizophrenia still leads to an alarming increase in natural and unnatural mortality.

Conclusions: Schizophrenia in combination with younger age, female sex, comorbid connective tissue disease, or major organ problems necessitates more tailored countermeasures to lessen the higher mortality risk in these patients compared with patients who have these characteristics and conditions but do not have schizophrenia.

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Many studies have noted that people with schizophrenia have greater mortality than expected or premature death compared with the general population or individuals without schizophrenia.[1–9] For example, an early Taiwanese inpatient epidemiologic study revealed that the all-cause mortality rate for male and female individuals with schizophrenia was 2.7 and 4.7 times, respectively, that of the sex-matched general population.[7] Saha et al,[6] in their systematic analysis of 37 studies, concluded that people with schizophrenia had a 2.58 times higher all-cause mortality rate than the general population. They also revealed a nearly 13 times higher suicide mortality rate in people with schizophrenia than in the general population.[6] Generally speaking, people with schizophrenia have a shortened life expectancy, with a reduction of approximately 10–15 potential life years.[3,8,9]

People with schizophrenia are often prone to behaviors linked to mortality, such as smoking, physical inactivity, poor diet, and substance use, and are less likely to seek health care services.[10–14] However, people with schizophrenia are also more vulnerable to many chronic physical illnesses, such as metabolic syndrome and cardiovascular diseases, than the general population, which might be attributable to the interaction between the aforementioned behaviors, shared genetic disposition, and treatment with second-generation antipsychotics.[11,15–18]

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Clinical Points

- Many studies have noted the high suicide incidence in people with schizophrenia, while accidental death receives less attention.
- The methodology of past research on cause-specific mortality has seldom examined how physical diseases such as AIDS and connective tissue disease affect schizophrenia's various forms of mortality.
- Given the rising comparative mortality risk, schizophrenia with younger age, female sex, or concurrent connective tissue and major organ diseases needs more attention and action.

Notably, although a gradual decline in age-standardized mortality rates has been observed in many countries, people with schizophrenia seem not to have benefited from advances in treatment and the preventive management of physical illness compared with the general population. This differential all-cause mortality gap between those with schizophrenia and the general population has gradually widened[1,5,6,9,19] or remained static.[1–3] Hence, studying the link between schizophrenia and physical disorders and excess mortality may reveal modifiable risk factors to lower the mortality gap. However, certain mortality studies may be limited by sample size, utilization of only community-based or hospital-based samples, use of data from one location in a country, limited identification of physical illnesses, or presentation of results by considering the mental problem in its entirety.[6,10,20–23] Until now, only a few nationwide population-based studies have focused on excess mortality in schizophrenia and its relationship with other chronic physical conditions beyond cancer and cardiovascular diseases.[1,4,11,24]

In addition, the majority of the previous research has focused on cause-specific mortality for various physical illnesses in people with schizophrenia,[1,2,4,10,11,21,24,25] rather than on the effect of schizophrenia on the mortality of individuals with specific physical illnesses, which may further emphasize the role of general practitioners and other specialists in reducing mortality in schizophrenia. Many physical illnesses exhibit similar therapeutic challenges to schizophrenia. For example, antiretroviral therapy may lower HIV-related mortality among AIDS patients, who have greater morbidity, suicide, and death rates than the general population.[26–29] Nevertheless, stigma, forgetfulness, lack of awareness of therapeutic benefits, and drug-related side effects make HIV medication adherence difficult, leading to increased natural and suicide mortality in patients living with HIV.[28] Surprisingly, a population-based cohort study revealed no correlation between a schizophrenia diagnosis and mortality in HIV patients.[30] Hence, studying the effect of schizophrenia on the mortality of individuals with other physical illnesses, not physical cause–specific mortality, may shed more light on the high death rate associated with schizophrenia.

Notably, there have been very few comprehensive reports on the accidental death of people with schizophrenia. It also remains unclear whether the disparity in accidental mortality between people with schizophrenia and the general population has diminished over time. Using the National Health Insurance Research Database (NHIRD) of Taiwan and National Mortality Registry with data relating to approximately 26 million individuals in Taiwan, we comprehensively examined the various mortality risks of people with and without schizophrenia using inpatient and outpatient records. In addition, risk estimates related to age, sex, and physical comorbidities were stratified to analyze their separate impact on the mortality of schizophrenia and non-schizophrenia groups to identify particularly vulnerable groups for future interventions.

METHODS

Data source. The Taiwan National Health Insurance (NHI) program, established in 1995, is a compulsory and universal single-payer health care insurance program that provides coverage to nearly all residents of Taiwan. NHI ensures low-cost and equal access to health service for every insured person, and its coverage rate was about 99.6%. The NHIRD contains comprehensive information about the insured individuals, including demographics and claims data (outpatient and inpatient care, medical diagnoses). The *International Classification of Diseases,* Ninth or Tenth Revision, Clinical Modification (*ICD-9-CM* [2003–2014] or *ICD-10-CM* [2015–2017]) were used for diagnosing diseases in the database. Our study was approved on a restricted basis to link the Longitudinal Health Insurance Database of the NHIRD with the Database of National Mortality Registry for the death causes and date of death. Both databases recorded information for the entire Taiwanese population (n = 26,554,001) between January 1, 2003, and December 31, 2017 (Supplementary Figure 1). From the National Mortality Registry, all-cause, natural, and unnatural (accident and suicide) mortality were identified (Supplementary Appendix 1). All analyses were conducted in the Health and Welfare Data Science Center, Ministry of Health and Welfare, Taiwan. The institutional review board of a local hospital approved the study protocol and waived the requirement for informed consent since this investigation used deidentified data and no human subjects contact was required.

Inclusion Criteria for Patients With Schizophrenia and Assessment of Physical Covariates

Patients diagnosed at least twice with schizophrenia or schizoaffective disorder (*ICD-9-CM* codes: 295 or *ICD-10-*

Table 1.

Demographic Characteristics of Individuals With and Without Schizophrenia in Taiwan

	Non-schizophrenia (n = 26,362,448)	Schizophrenia (n = 191,553)	*P* value
Sex, male, n (%)	13,359,396 (50.7)	100,037 (52.2)	<.001
Birth year, n (%)			<.001
1950 or before	4,679,622 (17.8)	23,135 (12.1)	
1951–1960	3,492,608 (13.3)	36,328 (19.0)	
1961–1970	3,868,927 (14.7)	49,169 (25.6)	
1971–1980	3,974,125 (15.1)	45,044 (23.5)	
1981–1990	3,575,992 (13.6)	27,872 (14.6)	
1991 or after	6,771,174 (25.5)	10,005 (5.2)	
CCI, n (%)			<.001
0	10,055,607 (38.2)	46,497 (24.3)	
1–2	9,686,037 (36.7)	74,799 (39.0)	
>2	6,620,804 (25.1)	70,257 (36.7)	

Abbreviation: CCI = Charlson Comorbidity Index.

Table 2.

Mortality Risk From Various Causes in Individuals With and Without Schizophrenia

Event	No. of events	Person-years	Mortality rate per 1,000 person-years	Adjusted HR (95% CI)[a]	*P* value
All cause					
SCZ	28,157	2,697,849.1	10.44	2.13 (2.11–2.16)	**<.001**
Non-SCZ	2,189,328	358,315,304.5	6.11	1.00 (ref)	
Natural					
SCZ	21,163	2,697,849.1	7.84	2.05 (2.02–2.08)	**<.001**
Non-SCZ	2,013,094	358,315,304.5	5.62	1.00 (ref)	
Unnatural					
SCZ	6,994	2,697,849.1	2.59	5.55 (5.42–5.68)	**<.001**
Non-SCZ	176,234	358,315,304.5	0.49	1.00 (ref)	
Accident					
SCZ	2,011	2,697,849.1	0.75	2.81 (2.68–2.93)	**<.001**
Non-SCZ	101,647	358,315,304.5	0.28	1.00 (ref)	
Suicide					
SCZ	3,695	2,697,849.1	1.37	9.57 (9.25–9.89)	**<.001**
Non-SCZ	52,720	358,315,304.5	0.15	1.0 (ref)	

[a]Adjusted by sex, birth year, and Charlson Comorbidity Index group.
Abbreviations: HR = hazard ratio, SCZ = schizophrenia.

CM codes: F20, F25) by board-certified psychiatrists were included as the schizophrenia cohort. For investigating the influence of physical comorbidities on mortality, Charlson Comorbidity Index (CCI) was evaluated to determine the systemic health condition of all enrolled subjects.[31] Further, Charlson comorbidity illnesses were grouped into 8 specific categories, ie, circulatory disease, liver disease, diabetes, chronic obstructive pulmonary disease, connective tissue diseases, renal disease, neoplasm, and AIDS, to understand the effect of schizophrenia on mortality in patients with different system diseases (detailed definitions in Supplementary Table 1).

Statistical Methods

Independent *t* tests and Pearson χ^2 tests were conducted to compare patients with and without schizophrenia. The main outcomes were all-cause mortality and 4 cause-specific mortality types including natural cause, unnatural cause, accident, and suicide. Cox proportional hazard models were used to evaluate the risk of mortality for patients with schizophrenia. After adjustment for age, sex, urbanization level, and CCI, adjusted hazard ratios and 95% confidence intervals were calculated. Four subanalyses stratified by age (0–20 years, 21–40 years, 41–60 years, > 60 years), sex (male, female), CCI (0, 1–2, > 2), and 8 Charlson comorbidities were further performed to determine these covariate influences on mortality. A test of interactions of subgroups with schizophrenia was performed. To explore the cohort trends for mortality among schizophrenia patients, these 5 mortality risks in 3 calendar-defined cohorts (2000, 2005, and 2010) were calculated. To further assess the robustness of our results and minimize the influence of potential bias, we also performed a 1:4 exact-matched controlled study to reduce the influence of age and sex. The stratified Cox proportional hazard was used for matched-pair cohort.[32] The significance level was set at < .05, and all statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC).

RESULTS

We identified 26,362,448 individuals without schizophrenia from the database (50.7% male) and 191,553 individuals with schizophrenia (52.2% male) from between 2003 and 2017 (Supplementary Figure 1). The schizophrenia group had significantly higher comorbidities than the non-schizophrenia group, as presented in Table 1. During the study period, 28,157 deaths (14.7%) over 2.7 million person-years of follow-up were observed among schizophrenia patients, whereas 2.2 million deaths (8.7%) over 358 million person-years of follow-up were observed for the non-schizophrenia group. Mortality rates (per 1,000 person-years) were 10.44 and 6.11 for schizophrenia and non-schizophrenia, respectively (Table 2).

Compared with the non-schizophrenia group, schizophrenia was associated with a higher risk of all-cause mortality after adjustments for sex, birth year, and CCI scores (adjusted hazard ratio [aHR] = 2.13; 95% confidence interval [CI], 2.11–2.16; *P* < .001). The risks of natural and unnatural death were both significantly elevated in patients with schizophrenia. In particular, the suicide mortality risk among patients with schizophrenia was approximately 10 times that of people without schizophrenia (aHR = 9.57; 95% CI, 9.25–9.89; *P* < .001; Table 2). Compared with the non-schizophrenia group in the same age subgroup, the schizophrenia group demonstrated the highest comparative risks of all-cause, natural, unnatural, and accidental death in the 21–40 age group and the lowest comparative risk

of these types of mortality in the > 60 age group (all-cause: age 21–40, aHR = 3.34; age > 60, aHR = 1.71; Table 3). Schizophrenia in the youngest age group demonstrated the highest comparative suicidal mortality risk than the same age group without schizophrenia, and the gap in suicide mortality risk between schizophrenia and non-schizophrenia declined gradually with increasing age (age ≤ 20, aHR = 15.55; age > 60, aHR = 1.52; *P* for trend, < .001).

Compared with females without schizophrenia, females with schizophrenia had greatly increased risks of mortality from various causes (eg, natural death, aHR = 2.41; suicide death, aHR = 11.82), and the disparities between those with and without schizophrenia were relatively larger than in the male group (eg, natural death, aHR = 2.19; suicide death, aHR = 8.11, all *P* values for sex interaction were < .001; Supplementary Table 2). It is noteworthy that the various absolute mortality rates were still consistently higher for male than female individuals with schizophrenia. The schizophrenia effects on various comparative mortality risks, except accidental mortality, declined with increasing physical comorbidities (all-cause death, CCI = 0, aHR = 4.95; CCI = 1–2, 3.63; CCI = 2, 1.66; *P* for trend, < .001; suicide death, CCI = 0, 15.22; CCI = 1–2, 10.33; CCI = 2, 4.84; *P* for trend, < .001) (Supplementary Table 3). However, the absolute all-cause mortality rates still gradually increased with increasing physical comorbidities. These findings remained robust in the 1:4 age- and sex-matched case-control analysis (Supplementary Tables 4–8).

The effects of schizophrenia on mortality in individuals without a specific physical illness were more hazardous than in those with the specific physical illness (Table 4), implying again that the schizophrenia effect played a more important role in an individual with relatively better physical health. Among individuals with neoplasm, those with schizophrenia had only a modestly higher natural mortality than those without schizophrenia (aHR = 1.33). In contrast, the schizophrenia effect still considerably raised the natural mortality of people with connective tissue diseases, chronic lung and liver diseases, and diabetes. In particular, a diagnosis of schizophrenia contributed to the comparatively elevated accidental death and suicide risks among those with connective tissue disease compared to those with the other 7 CCI categories. In comparing schizophrenia and no schizophrenia, the disparity between the two groups in suicide mortality among individuals with AIDS was comparatively

Table 3.
Mortality Risk From Various Causes in Individuals With and Without Schizophrenia, Stratified by Age[a]

		Age 0–20 y			Age 21–40 y			Age 41–60 y			Age > 60 y				
		No. of events	Mortality rate per 1,000 person-years	Adjusted HR (95% CI)[b]	No. of events	Mortality rate per 1,000 person-years	Adjusted HR (95% CI)[b]	No. of events	Mortality rate per 1,000 person-years	Adjusted HR (95% CI)[b]	No. of events	Mortality rate per 1,000 person-years	Adjusted HR (95% CI)[b]	Interaction of age and group	*P* for trend
All cause															
	SCZ	707	1.79	2.50 (2.25–2.78)	8,244	6.28	3.34 (3.25–3.43)	12,755	14.82	2.57 (2.53–2.62)	6,451	50.41	1.71 (1.67–1.76)	χ^2 = 1360.56	χ^2 = 373.76
	Non-SCZ	33,597	0.35	1.00 (ref)	174,633	1.49	1.00 (ref)	518,414	5.90	1.00 (ref)	1,453,753	38.13	1.00 (ref)	*P* < .001	*P* < .001
Natural															
	SCZ	166	0.42	2.78 (2.38–3.24)	4,368	3.33	3.04 (2.95–3.13)	10,439	12.13	2.50 (2.45–2.55)	6,190	48.37	1.71 (1.67–1.76)	χ^2 = 876.30	χ^2 = 74.54
	Non-SCZ	14,497	0.15	1.00 (ref)	122,239	1.04	1.00 (ref)	463,319	5.27	1.00 (ref)	1,405,682	36.87	1.00 (ref)	P < .001	P < .001
Unnatural															
	SCZ	541	1.37	5.28 (4.85–5.75)	3,876	2.95	6.51 (6.3–6.73)	2,316	2.69	4.39 (4.21–4.57)	261	2.04	1.67 (1.48–1.89)	χ^2 = 566.99	χ^2 = 584.48
	Non-SCZ	19,100	0.20	1.00 (ref)	52,394	0.45	1.00 (ref)	55,095	0.63	1.00 (ref)	48,071	1.26	1.00 (ref)	P < .001	P < .001
Accident															
	SCZ	87	0.22	1.27 (1.03–1.56)	923	0.70	3.25 (3.04–3.47)	845	0.98	2.99 (2.79–3.2)	156	1.22	1.52 (1.29–1.77)	χ^2 = 107.92	χ^2 = 9.20
	Non-SCZ	13,364	0.14	1.00 (ref)	25,073	0.21	1.00 (ref)	29,866	0.34	1.00 (ref)	32,209	0.84	1.00 (ref)	P < .001	P < .001
Suicide															
	SCZ	359	0.91	15.55 (13.95–17.34)	2,169	1.65	10.02 (9.59–10.48)	1,106	1.29	6.31 (5.94–6.7)	61	0.48	1.52 (1.19–1.96)	χ^2 = 579.62	χ^2 = 521.16
	Non-SCZ	3,736	0.04	1.00 (ref)	19,048	0.16	1.00 (ref)	18,134	0.21	1.00 (ref)	11,801	0.31	1.00 (ref)	P < .001	P < .001

[a]Age defined in 2004.
[b]Adjusted by sex and Charlson Comorbidity Index group.
Abbreviations: HR = hazard ratio, SCZ = schizophrenia.

Table 4.
Various Mortality Causes With Comorbid Somatic Illness and Schizophrenia

Comorbid physical condition		No. of individuals	Adjusted HR[a] of schizophrenia group (95% CI)				
			All cause	Natural	Unnatural	Accident	Suicide
Neoplasm	Yes	2,151,319	1.36 (1.32–1.39)	1.33 (1.30–1.37)	3.62 (3.22–4.07)	3.21 (2.66–3.87)	3.94 (3.32–4.67)
	No	24,402,682	3.09 (3.05–3.14)	3.09 (3.04–3.14)	5.36 (5.23–5.49)	2.63 (2.51–2.75)	9.74 (9.42–10.08)
Circulatory disease	Yes	4,361,852	1.86 (1.83–1.90)	1.83 (1.80–1.87)	2.76 (2.60–2.92)	2.00 (1.84–2.18)	4.22 (3.85–4.64)
	No	22,192,149	2.88 (2.83–2.93)	2.75 (2.70–2.80)	6.19 (6.03–6.36)	2.85 (2.71–3.01)	10.95 (10.56–11.35)
Diabetes mellitus	Yes	4,311,242	2.13 (2.09–2.18)	2.06 (2.02–2.11)	4.12 (3.90–4.36)	2.82 (2.57–3.09)	5.42 (4.99–5.89)
	No	22,242,759	2.59 (2.55–2.63)	2.48 (2.43–2.52)	5.91 (5.76–6.07)	2.80 (2.66–2.94)	10.88 (10.49–11.28)
AIDS	Yes	36,399	1.76 (1.48–2.09)	1.64 (1.35–1.99)	2.56 (1.90–3.45)	2.50 (1.56–4.00)	2.73 (1.70–4.39)
	No	26,517,602	2.37 (2.34–2.40)	2.28 (2.25–2.31)	5.31 (5.19–5.44)	2.66 (2.55–2.79)	9.33 (9.03–9.65)
COPD	Yes	8,597,242	2.22 (2.18–2.26)	2.14 (2.10–2.19)	4.89 (4.67–5.12)	3.03 (2.81–3.28)	7.19 (6.72–7.68)
	No	17,956,759	2.58 (2.53–2.62)	2.44 (2.40–2.49)	5.84 (5.68–6.00)	2.72 (2.58–2.87)	10.81 (10.4–11.24)
CKD	Yes	1,733,039	1.66 (1.61–1.72)	1.61 (1.56–1.67)	3.78 (3.40–4.20)	2.84 (2.41–3.35)	4.73 (4.01–5.58)
	No	24,820,962	2.56 (2.52–2.59)	2.47 (2.43–2.51)	5.40 (5.27–5.53)	2.66 (2.54–2.79)	9.60 (9.28–9.94)
Liver diseases	Yes	6,169,249	2.09 (2.05–2.13)	1.98 (1.94–2.02)	4.88 (4.67–5.09)	3.11 (2.89–3.34)	7.13 (6.71–7.58)
	No	20,384,752	2.56 (2.52–2.60)	2.49 (2.44–2.53)	5.68 (5.52–5.85)	2.59 (2.45–2.74)	10.65 (10.24–11.08)
Connective diseases	Yes	1,315,986	2.31 (2.17–2.45)	2.15 (2.02–2.29)	6.47 (5.73–7.30)	3.95 (3.14–4.97)	8.38 (7.12–9.86)
	No	25,238,015	2.37 (2.34–2.40)	2.29 (2.25–2.32)	5.27 (5.14–5.40)	2.64 (2.53–2.76)	9.33 (9.02–9.66)

[a]Adjusted by sex, birth year, and other Charlson comorbidities.
Abbreviations: CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, HR = hazard ratio.

lower than the disparity among individuals with other specific physical illness (suicide death, AIDS, aHR = 2.73; other 7 CCI categories, aHR = 3.94–8.38).

We also compared various mortality hazards in 3 calendar periods (2005, 2010, and 2015; Supplementary Table 9), indicating that the gap of natural and accidental mortality between schizophrenia and non-schizophrenia progressively increased from 2005 to 2015; by contrast, the gap of suicide mortality between two groups decreased modestly over time. The 2017 age pyramid for crude mortality rates for different causes stratified by 5-year intervals is presented in Figure 1.

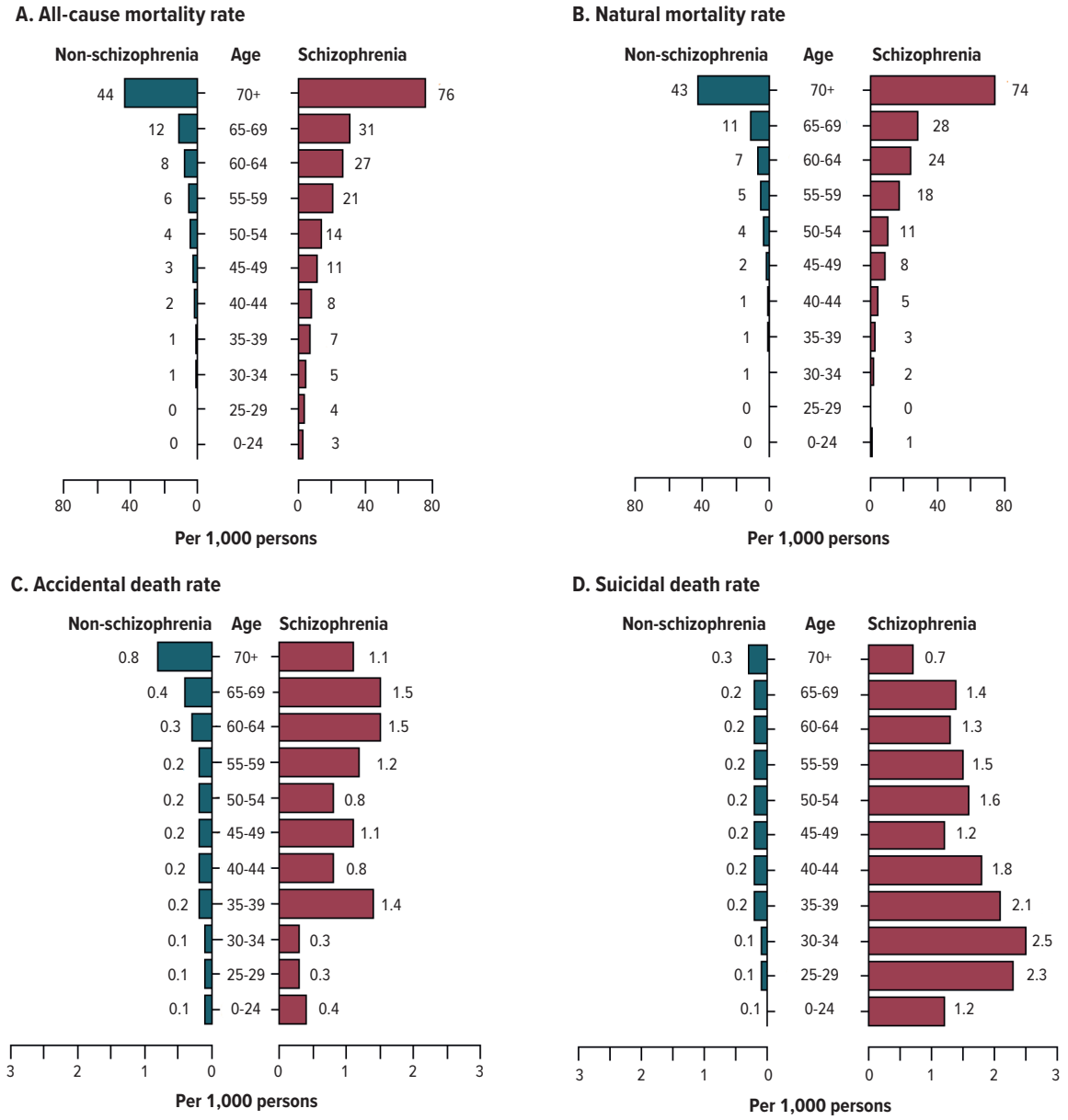
DISCUSSION

Our study was the largest in Asia and one of the largest and most comprehensive in the world to investigate the link between schizophrenia and mortality and to clarify the effects of age, sex, and comorbid physical conditions on the various causes of mortality in patients with schizophrenia. In this nationwide population-based cohort study of more than 26 million individuals over 358 million person-years of follow-up, approximately 200,000 patients with schizophrenia were identified, of whom nearly 30,000 died. The increased accidental mortality was distributed across the lifespan of patients with schizophrenia, and the hazard was gradually exacerbated over decades. In this study, we demonstrated that a diagnosis of schizophrenia causes greater comparative natural mortality risk in adolescents and young adults than older patients and greater comparative suicide mortality risk in women than men. We examined the association between Charlson comorbidities and schizophrenia in relation to various mortality causes, taking into consideration other comorbidities; hence, our results may be more reflective of real-world scenarios than those of other studies. Our results were robust, which was also verified by the age-matched and sex-matched case-control analyses. In addition, we expanded on pertinent knowledge regarding the different causes of death and physical illnesses among schizophrenia patients. To minimize mortality, clinicians and researchers should also pay attention to patients with schizophrenia and comorbid connective tissue disease, in addition to cardiovascular disease, chronic lung and liver problems, and diabetes.

The majority of research on schizophrenia and related mortality has come from Europe or North America.[33,34] The results of previous Asian studies on this topic may be influenced by their small sample sizes and possible sampling bias. The current study was the largest and most extensive investigation on this issue in Asia, and our findings were in line with previous research showing that people with schizophrenia had a 2- to-3-fold greater mortality risk than those without or the general population.[2,4,6,9,35] We revealed that female patients with schizophrenia had comparatively higher mortality increases for all-cause mortality than male patients with schizophrenia, which is consistent with the findings of population studies[4,25] but not with those of a large meta-analysis reporting no sex difference.[6] Suicide rates for men have been estimated to be roughly 3–4 times higher than for women in the general population, but the sex difference effect for suicide rate appears to be less prominent in patients with schizophrenia.[36] Suicide attempts, for example, did not differ between male and female patients

Figure 1.

Age Distribution of the Mortality Rates for Various Causes in Individuals With and Without Schizophrenia in Taiwan in 2017 (per 1,000 Individuals)[a]



[a]Patients with schizophrenia aged < 70 years had an approximately 4- to 5-fold higher accidental death rate and approximately 3-fold higher natural death rate than those without schizophrenia. Schizophrenia was associated with a 10- to 20-fold higher crude mortality rate for suicide in those aged < 45 years and a 7-fold higher crude mortality rate for suicide in those aged 45–69 years compared with non-schizophrenia.

with schizophrenia, in contrast to more non-lethal suicide behaviors in the general female population.[37] Consistent with this concept, even though suicide death rates for males with schizophrenia were still higher than for females with schizophrenia (1.57/1,000 person-years vs 1.15/1,000 person-years, respectively), the sex difference in suicide mortality rates declined from the non-schizophrenia to schizophrenia population (0.20/1,000 person-years vs 0.09/1,000 person-years, respectively) (Supplementary Table 2). Furthermore, societal prejudices, particularly in Asia, may exacerbate stressors associated with being female and having schizophrenia, such as marriage, pregnancy, childbirth, and infant care, echoing our findings of a considerably elevated HR of 11.82 in females with schizophrenia compared to females without schizophrenia.[38] This study further provides evidence of a statistical sex-based difference for mortality risk from different causes, highlighting that the schizophrenia effect

led to a relatively higher unnatural, suicide, and accidental mortality increase in female individuals than in males.

Those with schizophrenia but without any Charlson comorbidities had the highest mortality risk increase for natural causes and suicide. These findings were confirmed by our age- and sex-matched case-control analysis and therefore less likely to be explained by the interaction effect between age and CCI on mortality. Physical illnesses in patients with schizophrenia are common but usually underdetected and undertreated, which may explain the considerable mortality difference compared with the relatively more healthy individuals without schizophrenia among the subgroups with CCI = 0.[4,11,39] A forensic autopsy study revealed that 78.9% of sudden unexpected deaths in patients with schizophrenia could be attributed to cardiovascular diseases.[40] A Swedish study reported no excess cancer mortality and only modestly elevated ischemic heart disease mortality among patients with schizophrenia if detected early.[4] In our study, patients with schizophrenia below the age of 40, an age at which we typically disregard the likelihood of physical illness, were found to have a relatively high natural death rate, similar to the findings of high natural mortality rates for patients with schizophrenia aged below 40–50 in Danish and Swedish studies.[4,11] Psychiatrists and general practitioners might need to thoroughly check patients' physical condition, just as they do their psychiatric symptoms. Therefore, an aggressive care plan for secondary prevention (eg, regular metabolic and cancer screening from a young age) and tertiary prevention (eg, increasing adherence to standard treatment for physical illness) tailored to this population is urgently needed. See Supplementary Appendices 2 and 3 for further discussions on suicide mortality and the impact of CCI on mortality in people with schizophrenia.

Our study was the largest nationwide population-based study to comprehensively evaluate the impact of schizophrenia on mortality from different causes in patients with AIDS and connective tissue disease. By utilizing an insurance database with high coverage and thorough medical records, we were able to eliminate the sample, selection, and attrition biases that typically plague AIDS research. There have been few studies on the mortality risk of schizophrenia in people with AIDS, and their findings have been limited by the use of specialized group cohorts[41] or regional cohorts,[30,34] or sole examination of all-cause mortality.[30,42] We found that the schizophrenia effect on patients with AIDS led to a somewhat smaller increase in suicide mortality compared to other comorbidities. The explanation for this may be that patients who are HIV-positive, a powerful predictor of suicide, are 100 times more likely to commit suicide than the general population,[26] therefore diminishing the schizophrenia effect on suicidal death. In patients with AIDS and schizophrenia compared to patients with AIDS and no schizophrenia, the adjustment for other comorbidities in our study may have resulted in a relatively low risk (aHR = 1.76) of all-cause mortality compared to the findings of a Danish population-based study, which indicated a 3-fold higher risk of all-cause mortality.[42] Despite the fact that connective tissue disease is one of few physical illnesses underrepresented in schizophrenia,[11,39] recent investigations discovered the tight bidirectional relationship between schizophrenia and connective tissue diseases.[43,44] However, in decades, there have been only 2 investigations regarding mortality risk in patients with schizophrenia and connective tissue disease.[33] The results of the present study on connective tissue disease increased our understanding of this neglected topic. In contrast to those with the other 7 CCI comorbidities, we discovered that, in patients with connective tissue disease, a diagnosis of schizophrenia still contributes to the greater comparative mortality risk for natural causes, accidents, and suicide, which was not diminished by the illness (ie, connective tissue disease). Indeed, premature mortality was seen in individuals with connective tissue disorders.[45] Symptoms including joint pain, stiffness, and musculoskeletal discomfort may increase the risk of falls and fractures. Chronic pain and neuroendocrine dysregulation may be the determining variables in an elevated risk of suicide.[46] More research is required on the relationship between schizophrenia and connective tissue diseases and the rise in natural and unnatural mortality.

To our knowledge, the current study was also the largest one to clarify the relationship between physical illnesses and accidental mortality in patients with schizophrenia. Relative to the amount of research demonstrating the excess natural and suicide mortality among people with schizophrenia, less clinical and academic attention has been paid to the consequences of accidental death on mortality among these patients.[25,47,48] Fatigue, drowsiness, and impairments in attention, judgment, decision-making, and impulse control, which may result from the schizophrenia symptoms itself or from psychiatric medications, raise the risk of unsafe or reckless behaviors and accidental death among people with schizophrenia. Psychiatric medications may increase the risk of accidents due to the prevalent side effects, unintentional overdose, or purposeful overdose to relieve their symptoms.[47,49] In addition, social isolation may raise the risk of untreated injuries and accidental death among people with schizophrenia by limiting their access for help-seeking and medical care. In fact, Crump et al discovered that falls and accidental poisoning significantly contributed to the causes of accidental death among patients with schizophrenia.[47] Hellemose et al, in a Danish registry study, revealed an 8.3 to 10.5 times higher risk of accidental mortality among patients with schizophrenia, and the authors suggested that a Swedish study's findings of a 2.61 to 3.15 times higher hazard for accidental death might be confounded by the wide adjustment for sociodemographic variables.[47,48] However, in our population-based analysis with a 15-year follow-up, we found a 2.41- to 3.43-fold

greater risk of accidental mortality among individuals with schizophrenia, after adjusting solely for birth year and CCI score, confirming Swedish and American findings.[25,47] The current study investigated comprehensively the association between schizophrenia and accidental death, with a longer follow-up period, including participants aged 65 or older, and investigating the interaction of accidental death with age, CCI subgroups, and specific physical illnesses.[25,47,48] The results demonstrated that the schizophrenia effect might increase considerably the risk of accidental death in patients with connective tissue disease, neoplasms, and liver diseases. Further research to identify the causes of the increase in accidental mortality in people with these physical illnesses and schizophrenia is needed. Moreover, we found that female or middle-aged patients with schizophrenia had a significantly greater risk of accidental death, and the disparity of overall accidental death between patients with schizophrenia and those without increased with time. Our findings provide direction for designing further accident prevention strategies to reduce the excessive number of accidental deaths.

Some potential issues should be considered. First, only patients with schizophrenia who sought medical help between 2003 and 2017 were identified. Consequently, we might have missed some very mild cases of schizophrenia not identified by physicians or psychiatrists, or patients with very severe physical conditions that led to death before the diagnosis of schizophrenia during the 15-year observation period. However, schizophrenia is one of the most severe and chronic psychiatric disorders and often presents with several comorbidities; thus, the numbers of missed patients might be negligible. Second, data on education level, marital status, and smoking are unavailable in the NHIRD. We were therefore unable to assess their effects. However, studies have revealed that education level and marital status do not interact with all-cause mortality among patients with schizophrenia.[4] According to the literature, smoking cessation might attenuate mortality from circulatory and respiratory diseases by 10%–30% in patients with schizophrenia.[4,10] Third, our results represent the relationship between schizophrenia and mortality in a universal, convenient, and affordable health care system. Whether the excess mortality among patients with schizophrenia is higher in countries without a similar health care system remains undetermined.

The strength of the present cohort research lies in the use of the entire Taiwanese population as the sample, together with a long observation period, comprehensive medical data from outpatient and inpatient settings, and the entire age spectrum. We clarified the effects of age, sex, and concomitant physical conditions on natural, accidental, and suicide death in patients with schizophrenia, not for physical cause–specific mortality, thereby identifying schizophrenia-specific factors and not those actually associated with physical disease. Targeted preventive measures against these specific root factors may eventually minimize the excess mortality linked with schizophrenia.

CONCLUSION

This nationwide population-based cohort study in Taiwan comprehensively demonstrated the impact of several risk estimates on premature death among those with schizophrenia and confirmed the growing excess natural and accidental death among those with schizophrenia over time. More targeted countermeasures, such as those for accidental mortality and those focusing on younger age, female gender, and comorbid connective tissue illness, are crucial for decreasing schizophrenia mortality and need greater attention and action.

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Supplementary Material: Available at Psychiatrist.com.

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Supplementary Material

Article Title: Risk of All-Cause and Suicide Death in Patients With Schizophrenia: An Entire-Population Longitudinal Study in Taiwan

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

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Appendix 1: Data source.

The Taiwan National Health Insurance (NHI) program, established in 1995, is a compulsory and universal single-payer healthcare insurance, which provides to approximately entire residents of Taiwan. NHI ensures low-cost and equal access to health service for every insured person and its coverage rate was about 99.6%. The NHI Research Database (NHIRD) contains comprehensive information about the insured individuals, including demographics and claims data (date of birth, sex, outpatient and inpatient care, medical diagnoses). An anonymous identifier is assigned to every insured subject by the NHI institute to protect individual privacy before the data release. The International Classification of Diseases, 9th or 10th Revision, Clinical Modification (ICD-9-CM [2003-2014] or ICD-10-CM [2015-2017]) were used for diagnosing diseases in the database. Our study was approved restrictedly to link the Longitudinal Health Insurance Database of the NHIRD with the Database of National Mortality Registry for the death causes and date of death. Both databases recorded information for entire Taiwanese people (n = 26,554,001) between January, 1, 2003 and December, 31, 2017 (supplementary Figure S1). From the National Mortality Registry, all-cause, natural and unnatural (accident and suicide) mortality were identified. The NHIRD has been used in numerous epidemiological studies in Taiwan [24-27]. All analyses were conducted in the Health and Welfare Data Science Center, Ministry of Health and Welfare, Taiwan. Institutional review board of Taipei Veterans General Hospital approved the study protocol and waived the requirement for informed consent since this investigation used de-identified data and no human subjects contact was required.

Appendix 2: Suicide and schizophrenia

Similar to the findings of an American Medicare cohort study, we revealed that the comparative risk of suicide mortality among patients with schizophrenia decreased with age, but evidenced by using an entire national population, longer follow-up period, and all inpatient and outpatient records from the comprehensive lifetime national insurance program with a 99% coverage rate.[1] In our results, the youngest schizophrenia groups had the highest increase of suicide mortality, which is consistent with other findings.[1, 2] Previous studies have reported the suicide risk is highest during their early stage of schizophrenia (e.g., first episode, <2 years after the first episode of psychosis, or <5 years from diagnosis[3-5]. Due to the fast worsening in clinical and psychological aspects within the first 5 years, the critical period hypothesis may explain the phenomena of a greater risk of suicide in the early stages of schizophrenia compared to later stages.[6] Risk assessment programs and suicide prevention strategies tailored to the needs of people with schizophrenia are required, which should include assessment for previous suicidal symptoms, the treatment of comorbid substance use disorders, considering a clozapine regimen, family involvement from an early stage, and active use of long-acting injectable antipsychotics (LAI) from an early stage.[1, 7-11] Recently, a Taiwanese national cohort study provided evidence of a nearly 50% risk reduction in suicide mortality if patients switched to LAIs during the first 2 years of initiating antipsychotic treatment.[7] Although more physical comorbidities are considered a risk factor for suicide, this notion seems not to apply to individuals with schizophrenia but to non-schizophrenia. In tableS3, patients with schizophrenia and CCI>2 had a lower suicide mortality rate than those with no comorbidities, echoing the findings of the Medicare study that applied the Elixhauser Comorbidity Index.[1]

Appendix 3: CCI and schizophrenia

Those with schizophrenia but without any Charlson comorbidities had the highest mortality risk increase for natural causes and suicide. These findings were confirmed by our age-matched and sex-matched case–control analysis and therefore less likely to be explained by the interaction effect between age and CCI on mortality. Physical illnesses in patients with schizophrenia are common but usually underdetected and undertreated, which may explain the considerable mortality difference compared with the relatively more healthy individuals without schizophrenia among the subgroups with CCI=0.[12-14] A forensic autopsy study revealed that 78.9% of sudden unexpected deaths in patients with schizophrenia could be attributed to cardiovascular diseases.[15] Solmi et al in their recent meta-analysis study concluded patients with schizophrenia received less screening, less catheterization or revascularization in coronary artery disease or intravenous thrombolysis in stroke and treatment with specific medications for cardiovascular and cerebrovascular diseases.[16] Crump et al. reported the late diagnosis and suboptimal treatment of ischemic heart disease, cancer, and chronic obstructive pulmonary disease in people with schizophrenia, despite these patients having more times medical service contact than those without schizophrenia.[13] Moreover, a Swedish study reported no excess cancer mortality and only modestly elevated ischemic heart disease mortality among patients with schizophrenia if detected early.[13] Medical accessibility and medical cost might not be the core obstacle for elevated natural mortality in patients with schizophrenia. An increasing excess natural death incidence among these patients has been observed in both Taiwan and Denmark, whose health-care systems are easily accessible and either free or cheap. In Taiwan, patients even can access any specialist outpatient services anytime. In our study, patients with schizophrenia below the age of 40, an age at which we typically disregard the likelihood of physical illness, were found to have a relatively high natural death rate, similar to the findings of high natural mortality rates for patients with schizophrenia aged below 40-50 in Danish and Swedish studies.[12, 13] Psychiatrists and general practitioners might need to aggressively check patients' physical condition, just like their psychiatric symptoms. Therefore, an aggressive care plan for secondary (e.g., regular metabolic and cancer screening from a young age) and tertiary prevention (e.g., increasing the adherence to standard treatment for physical illness) tailored to this population is urgently needed.

Supplementary Table 1. Charlson comorbidities and eight specific illness categories derived from Charlson comorbidities

Condition Description	Points	Category	ICD-9-CM	ICD-10
Myocardial infarction	1	Circulatory disease	410.x, 412.x	I21.x, I22.x, I25.2
Congestive heart failure	1	Circulatory disease	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.x	I09.9,I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0
Peripheral vascular disease	1	Circulatory disease	093.0, 437.3, 440.x, 441.x, 443.1-443.9, 447.1, 557.1, 557.9, V43.4	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular disease	1	Circulatory disease	362.34, 430.x-438.x	G45.x, G46.x, H34.0, I60.x-I69.x
Dementia	1	X	290.x, 294.1, 331.2	F00.x-F03.x, F05.1, G30.x, G31.1
Chronic pulmonary disease	1	Chronic obstructive pulmonary disease	416.8, 416.9, 490.x-505.x, 506.4, 508.1, 508.8	I27.8, I27.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3
Rheumatic disease	1	Connective diseases	446.5, 710.0-710.4, 714.0-714.2, 714.8, 725.x	M05.x, M06.x, M31.5, M32.x-M34.x, M35.1, M35.3, M36.0
Peptic ulcer disease	1	X	531.x-534.x	K25.x-K28.x
Liver disease, mild	1	Liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7	B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4
Diabetes without chronic complications	1	Diabetes	250.0-250.3, 250.8, 250.9	E10.0, E10.l, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Diabetes with chronic complications	2	Diabetes	250.4-250.7	E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7
Hemiplegia or paraplegia	2	x	334.1, 342.x, 343.x, 344.0-344.6, 344.9	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0-G83.4, G83.9
Renal disease	1	Renal disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0-583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x	I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18.x, N19.x, N25.0, Z49.0-Z49.2, Z94.0, Z99.2
Any malignancy	2	Neoplasm	140.x-172.x, 174.x-195.8, 200.x-208.x, 238.6	C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.x, C90.x-C97.x
Liver disease, moderate to severe	3	Liver disease	456.0-456.2, 572.2-572.8	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Metastatic solid tumor	6	Neoplasm	196.x-199.x	C77.x-C80.x
AIDS / HIV	6	AIDS	042.x-044.x	B20.x-B22.x, B24.x

Adapted by Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* Nov 2005;43(11):1130-1139

Supplementary Table 2. Mortality risk from various causes in individuals with and without schizophrenia, stratified by sex

	Male			Female			Interaction of sex and group
	Number of Event	Mortality rate per 1000 person-years	Adjusted HR (95% C.I.)[a]	Number of Event	Mortality rate per 1000 person-years	Adjusted HR (95% C.I.) [a]	
All-Cause							
SCZ	16482	11.80	2.26 (2.22-2.30)	11675	8.97	2.52 (2.48-2.57)	χ^2=27.247

non-SCZ	1334763	7.43	1.00 (ref.)	854565	4.78	1.00 (ref.)	p<0.001
Natural							
SCZ	12127	8.69	2.19 (2.15-2.23)	9036	6.94	2.41 (2.36-2.46)	χ^2=23.607
non-SCZ	1207927	6.72	1.00 (ref.)	805167	4.51	1.00 (ref.)	p<0.001
Unnatural							
SCZ	4355	3.12	4.56 (4.42-4.70)	2639	2.03	7.16 (6.89-7.45)	χ^2=299.057
non-SCZ	126836	0.71	1.00 (ref.)	49398	0.28	1.00 (ref.)	p<0.001
Accident							
SCZ	1352	0.97	2.41 (2.28-2.54)	659	0.51	3.43 (3.17-3.70)	χ^2=42.437
non-SCZ	75207	0.42	1.00 (ref.)	26440	0.15	1.00 (ref.)	p<0.001
Suicide							
SCZ	2197	1.57	8.11 (7.77-8.47)	1498	1.15	11.82 (11.21-12.46)	χ^2=118.367
non-SCZ	35948	0.20	1.00 (ref.)	16772	0.09	1.00 (ref.)	p<0.001

a. Adjusted by birth year and Charlson Comorbidity Index (CCI) group

Supplementary Table 3. Mortality risk from various causes in individuals with and without schizophrenia, stratified by comorbidity level

	CCI=0			CCI=1,2			CCI>2				
	Number of Event	Mortality rate per 1000 person-years	Adjusted HR (95% C.I.) [a]	Number of Event	Mortality rate per 1000 person-years	Adjusted HR (95% C.I.) [a]	Number of Event	Mortality rate per 1000 person-years	Adjusted HR (95% C.I.) [a]	Interaction of CCI and group	P for trend
All Cause											
SCZ	4333	6.54	4.95 (4.77-5.13)	7487	6.99	3.63 (3.54-3.73)	16337	16.93	1.66 (1.64-1.69)	p<0.001	p<0.001
non-SCZ	139823	1.04	1.00 (ref.)	300154	2.20	1.00 (ref.)	1749351	19.99	1.00 (ref.)		
Natural											
SCZ	1914	2.89	5.94 (5.68-6.22)	4710	4.40	3.62 (3.52-3.73)	14539	15.07	1.61 (1.58-1.64)	p<0.001	p<0.001
non-SCZ	76426	0.57	1.00 (ref.)	243319	1.78	1.00 (ref.)	1693349	19.35	1.00 (ref.)		
Unnatural											
SCZ	2419	3.65	7.19 (6.90-7.49)	2777	2.59	5.94 (5.72-6.17)	1798	1.86	3.80 (3.63-3.99)	p<0.001	p<0.001
non-SCZ	63397	0.47	1.00 (ref.)	56835	0.42	1.00 (ref.)	56002	0.64	1.00 (ref.)		
Accident											
SCZ	545	0.82	2.79 (2.56-3.03)	771	0.72	2.91 (2.71-3.12)	695	0.72	2.83 (2.63-3.05)	p=0.7712	na
non-SCZ	36850	0.27	1.00 (ref.)	32811	0.24	1.00 (ref.)	31986	0.37	1.00 (ref.)		
Suicide											
SCZ	1420	2.14	15.22 (14.42-16.07)	1466	1.37	10.33 (9.79-10.89)	809	0.84	4.84 (4.51-5.20)	p<0.001	p<0.001
non-SCZ	17621	0.13	1.00 (ref.)	17002	0.12	1.00 (ref.)	18097	0.21	a.0 ref.)		

a. Adjusted by birth year and sex; CCI= Charlson Comorbidity Index; na.: not available.

Supplementary Table 4. Demographic characteristics of individuals with schizophrenia and age-matched and sex-matched cohorts in Taiwan

	Matched groups (n=766,108)	Schizophrenia (n=191,527)	P value
Sex, n(%)			
Male	400,140 (52.2)	100,035 (52.2)	--
Female	365,968 (47.8)	91,492 (47.8)	
Birth Year, n (%)			--
-1950	82,856 (10.8)	20,714 (10.8)	
1951-1960	137,432 (17.9)	34,358 (17.9)	
1961-1970	194,648 (25.5)	48,662 (25.5)	
1971-1980	183,088 (23.9)	45,772 (23.9)	
1981-1990	120,500 (15.7)	30,125 (15.7)	
1991-	47,584 (6.2)	11,896 (6.2)	
CCI, n(%)			<0.001
0	258,840 (33.8)	46,488 (24.3)	
1-2	297,938 (38.9)	74,791 (39.0)	
>2	209,330 (27.3)	70,248 (36.7)	

Abbreviation: CCI = Charlson Comorbidity Index

Supplementary Table 5. Mortality risk from various causes in individuals with schizophrenia and age-matched and sex-matched cohorts in Taiwan

Event	Number of Event	Person-years	Mortality rate per 1000 p/y	Adjusted HR (95% C.I.) [a]	p-value
All Cause					
SCZ	28155	2697464.9	10.44	2.24 (2.21-2.28)	***<0.001***
non-SCZ	45611	11184502.7	4.08	1.00 (ref.)	
Natural					
SCZ	21161	2697464.9	7.84	2.12 (2.08-2.15)	***<0.001***
non-SCZ	39638	11184502.7	3.54	1.00 (ref.)	
Unnatural					
SCZ	6994	2697464.9	2.59	5.28 (5.09-5.46)	***<0.001***
non-SCZ	5973	11184502.7	0.53	1.00 (ref.)	
Accident					
SCZ	2011	2697464.9	0.75	2.82 (2.67-2.99)	***<0.001***
non-SCZ	3194	11184502.7	0.29	1.00 (ref.)	
Suicide					
SCZ	3695	2697464.9	1.37	8.59 (8.13-9.08)	***<0.001***
non-SCZ	1949	11184502.7	0.17	1.00 (ref.)	

a. Adjusted by sex, birth year, Charlson Comorbidity Index (CCI) group

Supplementary Table 6. Mortality risk from various causes in individuals with schizophrenia and age-matched and sex-matched cohorts, stratified by sex

	Male			Female			Interaction of sex and group
	Number of Event	Mortality rate per 1000 person-years	Adjusted HR (95% C.I.) [a]	Number of Event	Mortality rate per 1000 person-years	Adjusted HR (95% C.I.) [a]	
All Cause							
SCZ	16482	11.80	2.33 (2.28-2.37)	11673	8.97	2.76 (2.69-2.83)	χ^2=89.49
non-SCZ	28851	4.97	1.00 (ref.)	16760	3.12	1.00 (ref.)	p<0.001
Natural							
SCZ	12127	8.69	2.26 (2.21-2.31)	9034	6.94	2.61 (2.54-2.68)	χ^2=54.83
non-SCZ	24353	4.19	1.00 (ref.)	15285	2.84	1.00 (ref.)	p<0.001
Unnatural							
SCZ	4355	3.12	4.06 (3.90-4.23)	2639	2.03	7.45 (6.99-7.94)	χ^2=243.59
non-SCZ	4498	0.77	1.00 (ref.)	1475	0.27	1.00 (ref.)	p<0.001
Accident							
SCZ	1352	0.97	2.29 (2.14-2.45)	659	0.51	3.92 (3.53-4.36)	χ^2=69.55
non-SCZ	2489	0.43	1.00 (ref.)	705	0.13	1.00 (ref.)	p<0.001
Suicide							
SCZ	2197	1.57	6.75 (6.31-7.23)	1498	1.15	10.58 (9.61-11.64)	χ^2=56.83
non-SCZ	1361	0.23	1.00 (ref.)	588	0.11	1.00 (ref.)	p<0.001

a. Adjusted by birth year and Charlson Comorbidity Index (CCI) group

Supplementary Table 7. Mortality risk from various causes in individuals with schizophrenia and age-matched and sex-matched cohorts, stratified by comorbidity levels

	CCI=0			CCI=1,2			CCI>2			Interaction of CCI and group	P for trend
	Number of Event	Mortality rate per 1000 p/y	Adjusted HR (95% C.I.) [a]	Number of Event	Mortality rate per 1000 p/y	Adjusted HR (95% C.I.) [a]	Number of Event	Mortality rate per 1000 p/y	Adjusted HR (95% C.I.) [a]		
All Cause											

SCZ	4333	6.55	5.28 (5.02-5.54)	7487	6.99	4.14 (4.00,4.29)	16335	16.93	1.69 (1.66,1.72)	χ^2=3330.44	χ^2=12346.94
non-SCZ	4189	1.09	1.00 (ref.)	7000	1.59	1.00 (ref.)	34422	11.77	1.00 (ref.)	p<0.001	p<0.001
Natural											
SCZ	1914	2.89	7.21 (6.75-7.70)	4710	4.40	4.10 (3.94,4.27)	14537	15.07	1.64 (1.61,1.67)	χ^2=3096.17	χ^2=15137.94
non-SCZ	1799	0.47	1.00 (ref.)	4985	1.13	1.00 (ref.)	32854	11.23	1.00 (ref.)	p<0.001	p<0.001
Unnatural											
SCZ	2419	3.65	5.92 (5.59-6.26)	2777	2.59	5.85 (5.52,6.19)	1798	1.86	3.63 (3.39,3.89)	χ^2=128.57	χ^2=935.75
non-SCZ	2390	0.62	1.00 (ref.)	2015	0.46	1.00 (ref.)	1568	0.54	1.00 (ref.)	p<0.001	p<0.001
Accident											
SCZ	545	0.82	2.45 (2.22-2.71)	771	0.72	3.10 (2.83,3.40)	695	0.72	2.81 (2.54,3.11)	χ^2=9.50	χ^2=275.31
non-SCZ	1304	0.34	1.00 (ref.)	1067	0.24	1.00 (ref.)	823	0.28	1.00 (ref.)	p=0.0086	p<0.001
Suicide											
SCZ	1420	2.15	10.94 (10.02,11.95)	1466	1.37	9.21 (8.41,10.1)	809	0.84	4.73 (4.23,5.28)	χ^2=129.79	χ^2=510.32
non-SCZ	758	0.20	1.00 (ref.)	669	0.15	1.00 (ref.)	522	0.18	1.00 (ref.)	p<0.001	p<0.001

a. Adjusted by birth year and sex

Supplementary Table 8. Mortality risk from various causes in individuals with schizophrenia and age-matched and sex-matched cohorts, stratified by age

	Age 0-20			Age 21-40			Age 41-60		
	Number of Event	Mortality rate per 1000 p/y	Adjusted HR (95% C.I.) [a]	Number of Event	Mortality rate per 1000 p/y	Adjusted HR (95% C.I.) [a]	Number of Event	Mortality rate per 1000 p/y	Adjusted HR (95% C.I.) [a]
All Cause									
SCZ	707	1.79	2.41 (2.11-2.75)	8243	6.28	3.17 (3.07-3.28)	12754	14.82	2.65 (2.59-2.71)
non-SCZ	687	0.43	1.00 (ref.)	8902	1.65	1.00 (ref.)	19648	5.43	1.00 (ref.)
Natural									
SCZ	166	0.42	2.74 (2.25-3.33)	4367	3.33	2.91 (2.80-3.02)	10438	12.13	2.58 (2.52-2.64)
non-SCZ	245	0.15	1.00 (ref.)	6264	1.16	1.00 (ref.)	17410	4.81	1.00 (ref.)

Unnatural									
SCZ	541	1.37	4.94 (4.36-5.60)	3876	2.95	6.05 (5.76-6.36)	2316	2.69	4.36 (4.11-4.62)
non-SCZ	442	0.28	1.00 (ref.)	2638	0.49	1.00 (ref.)	2238	0.62	1.00 (ref.)
Accident									
SCZ	87	0.22	1.21 (0.95-1.54)	923	0.70	2.93 (2.70-3.19)	845	0.98	3.01 (2.76-3.29)
non-SCZ	290	0.18	1.00 (ref.)	1296	0.24	1.00 (ref.)	1185	0.33	1.00 (ref.)
Suicide									
SCZ	359	0.91	13.83 (11.13-17.19)	2169	1.65	9.51 (8.81-10.27)	1106	1.29	6.31 (5.75-6.93)
non-SCZ	105	0.07	1.00 (ref.)	939	0.17	1.00 (ref.)	737	0.20	1.00 (ref.)

	Age >60			Interaction of age and group	P for trend
	Number of Event	Mortality rate per 1000 p/y	Adjusted HR (95% C.I.) [a]		
All Cause					
SCZ	6451	50.41	1.89 (1.83-1.94)	χ^2=581.79	χ^2=479.35
non-SCZ	16374	28.57	1.00 (ref.)	p<0.001	p<0.001
Natural					
SCZ	6190	48.37	1.89 (1.83-1.95)	χ^2=370.86	χ^2=252.25
non-SCZ	15719	27.43	1.00 (ref.)	p<0.001	p<0.001
Unnatural					
SCZ	261	2.04	1.79 (1.55-2.07)	χ^2=272.44	χ^2=142.25
non-SCZ	655	1.14	1.00 (ref.)	p<0.001	p<0.001
Accident					
SCZ	156	1.22	1.67 (1.39-2.00)	χ^2=79.37	χ^2=0.01
non-SCZ	423	0.74	1.00 (ref.)	p<0.001	P=0.9524
Suicide					
SCZ	61	0.48	1.61 (1.20-2.16)	χ^2=179.47	χ^2=95.25
non-SCZ	168	0.29	1.00 (ref.)	p<0.001	p<0.001

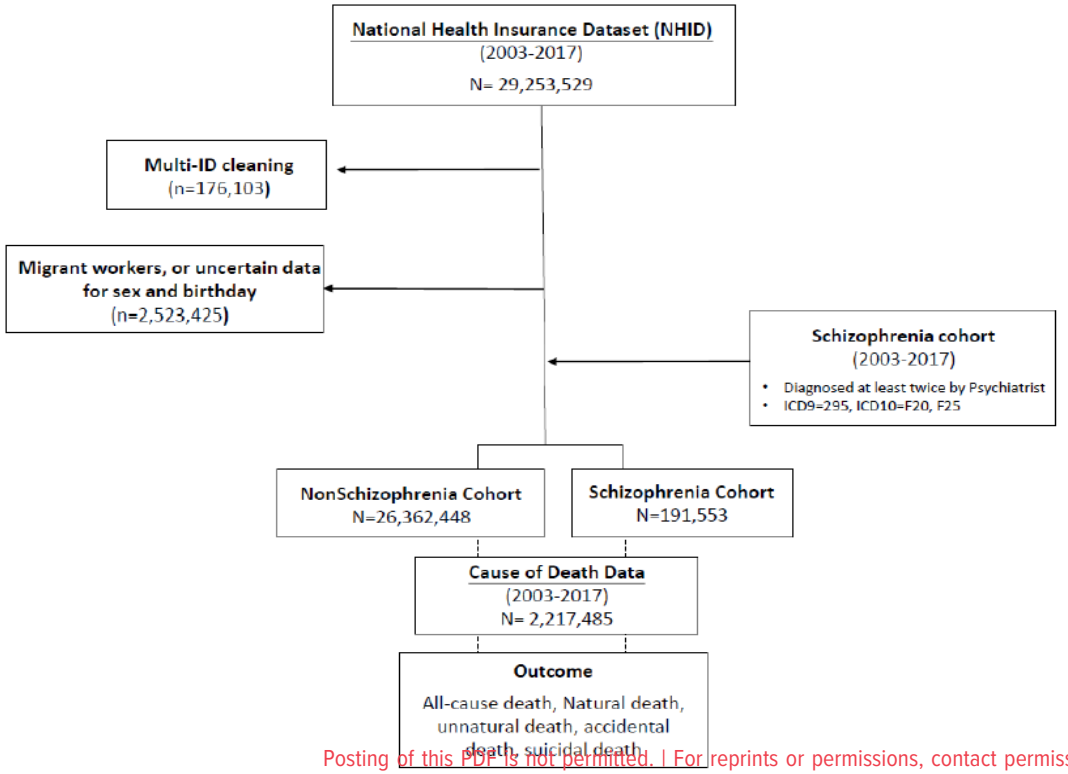
a. Age defined in 2004; Adjusted by sex and Charlson Comorbidity Index (CCI) group.

Supplementary Table 9. Mortality risk from various causes for patients with schizophrenia in three calendar periods

	Adjusted HR (95% C.I.) [a]				
	All Cause	Natural	Unnatural	Accident	Suicide
Cohort					
2005 cohort	2.24 (2.21-2.26)	2.15 (2.12-2.18)	5.68 (5.54-5.82)	2.94 (2.81-3.08)	9.48 (9.15-9.82)
2010 cohort	2.38 (2.34-2.41)	2.31 (2.27-2.34)	5.78 (5.60-5.97)	3.11 (2.94-3.30)	9.39 (8.98-9.82)
2015 cohort	2.48 (2.43-2.54)	2.41 (2.35-2.47)	5.84 (5.55-6.14)	3.40 (3.11-3.71)	9.09 (8.46-9.77)

a. Adjusted by sex, birth year, Charlson Comorbidity Index (CCI) group

Supplementary figure 1. Study flowchart



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