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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

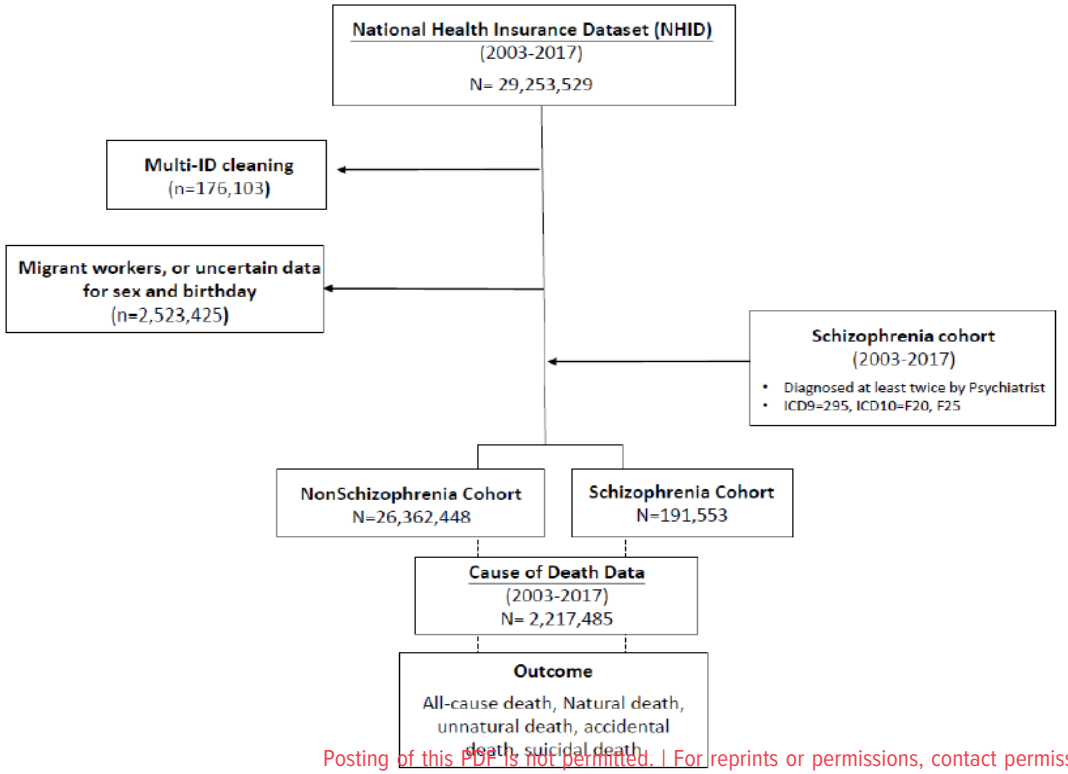
a. Age defined in 2004; Adjusted by sex and Charlson Comorbidity Index (CCI) group.

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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