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Age Effect on Incidence, Physical, and Psychiatric Comorbidity for Sudden Cardiac Death in Schizophrenia

Effet de l'âge sur l'incidence, la comorbidité physique et psychiatrique de la mort cardiaque subite dans la schizophrénie

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Abstract

Objective: The pathogenesis of sudden cardiac death may differ between younger and older adults in schizophrenia, but evidence remains scant. This study investigated the age effect on the incidence and risk of the physical and psychiatric comorbidity for sudden cardiac death.

Methods: Using 2000 to 2016 data from the Taiwan National Health Insurance Research Database and Department of Health Death Certification System, we identified a national cohort of 170,322 patients with schizophrenia, 1,836 of whom had a sudden cardiac death. Standardized mortality ratios (SMRs) were estimated. Hazard ratios and population attributable fractions of distinctive comorbidities for sudden cardiac death were assessed.

Results: The SMRs of sudden cardiac death were all >1.00 across each age group for both sexes, with the highest SMR in male patients aged <35 years (30.88, 95% CI: 26.18–36.18). The fractions of sudden cardiac death attributable to hypertension and congestive heart failure noticeably increased with age. By contrast, the fraction attributable to drug-induced mental disorder decreased with age. Additionally, chronic hepatic disease and sleep disorder increased the risk of sudden cardiac death in patients aged <35 years. Dementia and organic mental disorder elevated the risk in patients aged between 35–54 years. Ischemic heart disease raised the risk in patients aged ≥55 years.

Conclusions: The risk is increased across the lifespan in schizophrenia, particularly for younger male patients. Furthermore, physical and psychiatric comorbidities have age-dependent risks. The findings suggest that prevention strategies targeted toward sudden cardiac death in patients with schizophrenia must consider the age effect.

Abrégé

Objectif : La pathogenèse de la mort cardiaque subite peut différer entre adultes plus jeunes et plus âgés dans la schizophrénie, mais les données probantes demeurent faibles. La présente étude a recherché l'effet de l'âge sur l'incidence et le risque de morbidité physique et psychiatrique pour la mort cardiaque subite.

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Méthodes : À l'aide des données de 2000–2016 entre la Base de données nationale de recherche sur l'assurance maladie de Taïwan et le système de certification des décès du ministère de la santé, nous avons identifié une cohorte nationale de 170 322 patients souffrant de schizophrénie, dont 1 836 ont eu une mort cardiaque subite. Les taux de mortalité normalisés (TMN) ont été estimés. Les rapports de risques et les fractions attribuables à la population de comorbidités distinctes pour la mort cardiaque subite ont été évalués.

Résultats : Les TMN de la mort cardiaque subite étaient tous > 1,00 dans chaque groupe d'âge pour les deux sexes, et le TMN le plus élevé chez les patients masculins âgés < 35 ans était (30,88; IC à 95% 26,18 à 36,18). Les fractions de mort cardiaque subite attribuables à l'hypertension et à l'insuffisance cardiaque congestive ont augmenté visiblement avec l'âge. Par contre, la fraction attribuable à un trouble mental induit par les drogues diminuait avec l'âge. En outre, la maladie hépatique chronique et les troubles du sommeil augmentaient le risque de mort cardiaque subite chez les patients âgés < 35 ans. La démence et un trouble mental organique élevaient le risque chez les patients âgés entre 35 et 54 ans. La cardiopathie ischémique haussait le risque chez les patients âgés > 55 ans.

Conclusions : Le risque s'accroît au long de la durée de vie dans la schizophrénie, particulièrement chez les jeunes patients masculins. Par ailleurs, les comorbidités physiques et psychiatriques comportent des risques en fonction de l'âge. Les résultats suggèrent que des stratégies de prévention axées sur la mort cardiaque subite chez des patients souffrant de schizophrénie doivent tenir compte de l'effet de l'âge.

Keywords
schizophrenia, sudden cardiac death, age effect, incidence, standardized mortality ratio, population attributable fraction

Introduction

Schizophrenia is a severe mental illness that typically first manifests in adolescence or young adulthood.[1] During the illness course, patients with schizophrenia are at an increased risk of numerous physical and psychiatric comorbidities.[2-7] Furthermore, evidence has indicated that relative to the general population, patients with schizophrenia have an approximately 2 to 4 times higher mortality rate and an at least 10-year reduction in life expectancy.[4,8-10] In particular, cardiovascular diseases are the major physical comorbidities contributing to the risk of death in patients with schizophrenia, whether they be from Asia or the West.[4,9-11]

Among the causes of cardiovascular mortality, sudden cardiac death has recently received increasing attention given its nature of sudden circulatory collapse and considerable impact on public health.[12,13] However, currently, risk stratification for sudden cardiac death still remains imperfect,[12] which are possibly attributable to the heterogeneous etiologies of sudden cardiac death.[12,13] For instance, although ischemic heart disease is the most common cardiac pathology underlying sudden cardiac death, arrhythmia and cardiomyopathy actually account for significant proportions of sudden cardiac deaths in those young adults aged <35 years.[13] Considering the evidence of a distinctive distribution of etiologies for sudden cardiac death across the lifespan,[13] studies on the presumed mechanisms underlying sudden cardiac death must include age in their analysis.

Studies have suggested that patients with schizophrenia are at an increased risk of sudden cardiac death.[14-19] Notably, one postmortem study has found that myocardial infarction accounts for more than half of sudden deaths in older adult patients with schizophrenia.[16] By contrast, another postmortem study focusing on young adult patients revealed that >50% of sudden death cases remain unexplained, with arrhythmia as the suspected cause.[18] Considered together, these findings may imply an age effect on the pathogenesis and risk factors for sudden cardiac death in patients with schizophrenia. Thus far, only a few studies have directly examined the risk of physical and psychiatric comorbidities related to sudden cardiac death in patients with schizophrenia.[14,17] In these studies, dyslipidemia, diabetes mellitus, electrocardiographic abnormalities, and aggressive behaviors have been found to be associated with the risk of sudden cardiac death. However, the findings from these hospital-based studies, including ours, have potential selection bias as a shortcoming. Furthermore, these studies' small sample sizes yield results of limited statistical power, making it difficult to determine the effect of age on the association between risk of comorbidity and sudden cardiac death.

To fill this gap in the literature, this prospective national cohort study investigated 23 million Taiwanese adults to examine the age effect on the incidence and risk of the physical and psychiatric comorbidity for sudden cardiac death, we stratified the patients into 3 age subgroups: <35 (younger aged), 35 to 54 (middle aged), and ≥55 years (older aged) by adopting definitions from previous studies.[13,16,18,20]

Aims of the Study

To estimate the age effect on the incidence and standardized mortality ratio (SMR) of sudden cardiac death in patients with schizophrenia. In addition, we explored the age effect on the risk of the physical and psychiatric comorbidity for sudden cardiac death in schizophrenia. We hypothesized that distinctive comorbidities carry an age-dependent risk for sudden cardiac death in patients with schizophrenia.

Methods

Data Sources

The data source for this study was the entire Taiwan population (approximately 23,000,000 people) derived the

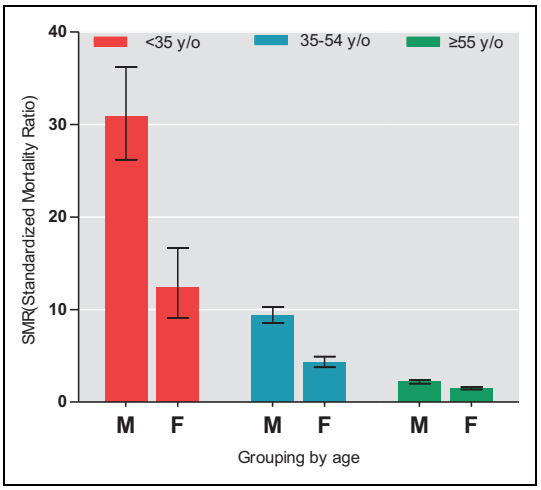

Figure 1. Standardized mortality ratios of sudden cardiac death across the lifespan in a nationwide schizophrenia cohort. [a]Error bars indicate 95% confidence intervals. [b]M: Male, F: Female.

National Health Insurance Research Database (NHIRD). The Institutional Review Board of Taipei City Hospital approved the protocol for this prospective nationwide cohort study, with a waiver of informed consent due to the de-identified and retrospective nature of the data.

The Taiwan NHIRD is maintained by the Health and Welfare Data Science Center and contains the registration files and medical claims data of beneficiaries who were covered by Taiwan's National Health Insurance (NHI). Taiwan's NHI program was implemented in 1995, and it provides comprehensive and accessible medical care to nearly 98% of the 23,000,000 Taiwanese population. The NHI covers visits to all NHI-contracted facilities in Taiwan, which makes the NHIRD database representative of the general population in Taiwan. Every year, the NHI authorities conduct a random review of the medical records to verify diagnosis codes. The Taiwan Joint Commission on Hospital Accreditation oversees the accreditation of most hospitals contracted with the NHI. To obtain accreditation for qualified psychiatric services, patients must receive a diagnosis from a board-certified psychiatrist. NHIRD claims' data have been a useful source of data for numerous peer-reviewed epidemiological studies because the database contains detailed information on diagnoses and treatment.[21-24]

Identification of Schizophrenia Cohort

We selected a cohort of patients from the Taiwan NHIRD database who received a mental disorder diagnosis (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes: 290.x to 319.x; International Classification of Diseases, Tenth Revision [ICD-10] codes: F01–F99) between January 1, 2000, and December 31, 2016 ($N = 10,422,350$; Supplemental Figure 1). We then excluded patients who received a diagnosis of mood disorder (ICD-9-CM code: 296.x) between January 1, 2000, and December 31, 2016 ($N = 188,902$). After the exclusion, patients who received a consistent diagnosis of schizophrenia (ICD-9-CM code: 295.x; ICD-10 code: F20.x) between January 1, 2001, and December 31, 2016 ($N = 170,322$) were included in the study cohort.

Identification of Sudden Cardiac Death Events

The data for each cohort member were electronically synced with the Department of Health's Death Certification System from January 1, 2001, through December 31, 2016, using the national identification number as an identifier (Supplemental Figure 1). Data on causes of death in the Department of Health's Death Certification System for dates before and after December 31, 2014, were grouped according to ICD-9-CM and ICD-10 categories, respectively. The ICD-9-CM codes that were used to define sudden cardiac death were 390 to 398, 402, and 404 to 429, as per previous studies.[17,25] The ICD-10 codes that were used to define sudden cardiac death were, as per Ray et al.,[26] I10, I11.9, I20, I21, I22, I23, I24, I25, I42.8, I42.9, I46, I47, I47.2, I49.0, I49.8, I49.9, I51.6, I51.9, I70.9, R96.1, and R98. In total, we identified 26,926 deaths, along with their causes of death. Among the 26,926 deaths, 1,836 were sudden cardiac deaths, defined to be so only if they were deaths reported as occurring out of hospital, or in the emergency room, or as "dead on arrival" with the cause of death reported to be cardiac disease.[17]

Statistical Analysis

We calculated the survival (contributed) time of each cohort member from the date of first diagnosis of schizophrenia (baseline) to either the event of sudden cardiac death or the end of study (December 31, 2016). The crude mortality rates for sudden cardiac death were calculated as the incident cases divided by the contributed person-years. The SMR was estimated using the ratio of observed sudden cardiac deaths in the schizophrenia cohort to the expected deaths in the general population of Taiwan by utilizing our previously described methods.[27] The expected number of sudden cardiac deaths was computed by multiplying the number in the study cohort (standardized by sex and age) by the national incidence of sudden cardiac death between January 1, 2001, and December 31, 2016. To explore the age effect on the incidence of sudden cardiac death in the schizophrenia cohort, we stratified patients into 3 age subgroups: <35 years, 35 to 54 years, and ≥55 years.[13,16,18,20]

Univariate Cox proportional hazards analyses were used to estimate the crude hazard ratios for each demographic and clinical variable. Using the backward stepwise selection method, we performed the multivariate Cox proportional hazards regression model to assess the hazard ratios for physical and psychiatric comorbidities. Variables with a significant association ($P < 0.001$) were retained in the final adjusted model. Furthermore, we calculated the population attributable fraction (PAF) by using the following equation:

Table 1. Incidence and Standardized Mortality Ratio of Sudden Cardiac Death ($N = 1,836$) in Patients with Schizophrenia ($N = 170,322$) Stratified by Age, from January 1, 2001, through December 31, 2016.

	N	Follow-up Duration, years: Mean (*SD*)	Number of Sudden Cardiac Death Observed (*N*)	Total Person-Years	Crude Incidence[a]	Expected Number (*N*)	SMR[b]	95% CI	*P*
Age[c] (years)									
<35	76,325	9.0 (4.7)	198	688,276.2	28.8	8.53	23.14	20.03 to 26.60	<0.001
35 to 54	61,453	8.1 (4.8)	665	500,483.2	132.9	98.90	6.73	6.22 to 7.26	<0.001
≥55	32,544	5.6 (4.5)	973	183,194.3	531.1	547.11	1.78	1.67 to 1.89	<0.001
Total	170,322	7.6 (4.5)	1,836	1,371,953.7	133.8	631.9	2.91	2.77 to 3.04	<0.001

[a]Incidence rate: incident number/100,000 person-years.
[b]Standardized mortality ratio (SMR): the observed number of cases with sudden cardiac death/expected number of cases; the expected numbers of sudden cardiac death was obtained by multiplying the cumulative contributed person-years of patients in the specified stratum of the cohort with schizophrenia by the incidence of sudden cardiac death (2001 to 2016) in the general population.
[c]Indicates age at the baseline; we calculated SMR based on sex- and period (year) adjustment.

prevalence of individual physical or psychiatric comorbidity in cases with sudden cardiac death × [(hazard ratio − 1)/ hazard ratio].[28] The hazard ratio of individual physical or psychiatric comorbidity on sudden cardiac death was estimated based on the final regression model.

All statistical analyses were conducted using SAS statistical software (SAS System for Windows, version 9.4, SAS Institute, Cary, NC, USA). A P value of <0.05 indicated statistical significance.

Results

Incidence and SMR of the Schizophrenia Cohort

The study cohort included 170,322 patients with schizophrenia. During the cohort follow-up of 7.6 ± 4.5 years, 1,836 patients with schizophrenia had sudden cardiac death. The crude incidence of sudden cardiac death in the schizophrenia cohort was 133.8 cases per 100,000 person-years (Table 1) and 28.8, 132.9, and 531.1 among patients aged <35, 35 to 54, and ≥55 years, respectively (Table 1; Supplemental Figure 2). In addition, the increase in the cumulative incidence of sudden cardiac death was significantly higher among male patients ($P < 0.001$) than among female patients (Supplemental Figure 3).

To estimate the risk of sudden cardiac death in patients with schizophrenia relative to the general population, SMRs were calculated. Significantly, the SMR of sudden cardiac death in the schizophrenia cohort was 2.91 (95% CI, 2.77 to 3.04; $P < 0.001$), which indicated a mortality gap between patients with schizophrenia and the general population. Furthermore, stratified analyses by age demonstrated that the SMRs of sudden cardiac death were all >1.00 across each age interval. The highest SMR was for patients aged <35 years (23.14; 95% CI, 20.03 to 26.60; $P < 0.001$), followed by those aged between 35 and 54 years (6.73; 95% CI, 6.22 to 7.26; $P < 0.001$) and those aged ≥55 years (1.78; 95% CI, 1.67 to 1.89; $P < 0.001$; Table 1). Additionally, stratified analyses by age and sex further revealed that male patients aged <35 years had the highest SMR (30.88; 95% CI, 26.18 to 36.18; Figure 1).

Demographic Risk Factors for Sudden Cardiac Death in Patients with Schizophrenia

Table 2 presents the Cox proportional hazards model of the demographic risk factors for sudden cardiac death in patients with schizophrenia. Compared to male patients with schizophrenia, female patients had a significantly lower risk of sudden cardiac death (0.58; 95% CI, 0.53 to 0.63; $P < 0.001$). In addition, relative to patients who were unemployed, patients who were employed had a reduced risk of sudden cardiac death (0.76; 95% CI, 0.69 to 0.84; $P < 0.001$). Conversely, as compared with those living in highly urbanized areas, patients with schizophrenia who lived in moderately urbanized areas (1.28; 95% CI, 1.14 to 1.43; $P < 0.001$), sub-rural areas (1.24; 95% CI, 1.07 to 1.45; $P = 0.005$), and rural areas (1.21; 95% CI, 1.04 to 1.41; $P = 0.014$) had a higher risk of sudden cardiac death.

Comorbidity Risk Factors for Sudden Cardiac Death in Patients with Schizophrenia

Table 3 presents the Cox proportional hazards model of the comorbidity risk factors for sudden cardiac death in patients with schizophrenia. Among physical comorbidities, hypertension (1.38; 95% CI, 1.23 to 1.55; $P < 0.001$), ischemic heart disease (1.30; 95% CI, 1.13 to 1.49; $P < 0.001$), and congestive heart failure (2.20; 95% CI, 1.87 to 2.58; $P < 0.001$) significantly increased the risk of sudden cardiac death in patients with schizophrenia. The proportions of sudden cardiac death that were attributable to hypertension, ischemic heart disease, and congestive heart failure were 9.91%, 3.98%, and 6.06%, respectively. As for psychiatric comorbidities, dementia and organic mental disorder (1.43; 95% CI, 1.24 to 1.64; $P < 0.001$) and drug-induced mental disorder (2.22; 95% CI, 1.78 to 2.77; $P < 0.001$) significantly increased the risk of sudden cardiac death in patients with schizophrenia; the fractions of sudden cardiac death attributable to the 2 aforementioned disorders were 3.73%, and 2.57%, respectively.

Table 2. Cox Proportional Hazards Model of Demographic Variables on the Risk of Sudden Cardiac Death in Patients with Schizophrenia.

Characteristics	Schizophrenia Cohort ($N = 170,322$) *N* (%)	Sudden Cardiac Death ($N = 1,836$) *N* (%)	Unadjusted Hazard Ratio	95% CI	*P*	Adjusted Hazard Ratio[a]	95% CI	*P*
Sex								
Male	87,839 (51.6)	1,072 (58.4)	Reference			Reference		
Female	82,483 (48.4)	764 (41.6)	0.76	0.69 to 0.84	<0.001	0.58	0.53 to 0.63	<0.001
Age, years								
<25	37,254 (21.9)	40 (2.2)	Reference			Reference		
25 to 34	39,071 (22.9)	158 (8.6)	4.00	2.83 to 5.66	<0.001	4.07	2.87 to 5.76	<0.001
35 to 44	34,919 (20.5)	319 (17.4)	9.42	6.78 to 13.09	<0.001	9.96	7.16 to 13.86	<0.001
45 to 54	26,534 (15.6)	346 (18.9)	14.76	10.64 to 20.47	<0.001	15.88	11.42 to 22.10	<0.001
55 to 64	15,402 (9.0)	314 (17.1)	27.32	19.66 to 37.97	<0.001	27.39	19.62 to 38.24	<0.001
65 to 74	8,225 (4.8)	267 (14.5)	49.88	35.77 to 69.56	<0.001	43.02	30.63 to 60.43	<0.001
≥75	8,917 (5.2)	392 (21.4)	113.41	81.79 to 157.26	<0.001	85.80	61.22 to 120.25	<0.001
Urbanization[b]								
Level 1	71,227 (41.8)	672 (36.6)	Reference			Reference		
Level 2	45,721 (26.8)	541 (29.5)	1.36	1.21 to 1.52	<0.001	1.28	1.14 to 1.43	<0.001
Level 3	18,543 (10.9)	180 (9.8)	1.03	0.87 to 1.21	0.727	0.98	0.83 to 1.16	0.836
Level 4	17,078 (10.0)	224 (12.2)	1.41	1.21 to 1.64	<0.001	1.24	1.07 to 1.45	0.005
Level 5	16,966 (10.0)	216 (11.8)	1.37	1.18 to 1.60	<0.001	1.21	1.04 to 1.41	0.014
Employment								
No	116,765 (68.6)	1,277 (69.6)	Reference					
Yes	53,557 (31.4)	559 (30.5)	0.96	0.87 to 1.06	0.420	0.76	0.69 to 0.84	<0.001

[a]Based on multivariate regression model: the variables in Table 2 (demographical information) and the variables in Supplemental Table 1 (physical and psychiatric comorbidities) with $P < 0.001$ were remained in the final adjusted model.

[b]We applied urbanization stratification specifically used in Taiwan, and the level of urbanization was categorized as Level 1 (highly urbanized area), Level 2 (moderately urbanized area), Level 3 (township area), Level 4 (subrural area), and Level 5 (rural area).

Table 3. Cox Proportional Hazards Model of Physical and Psychiatric Comorbidity on the Risk of Sudden Cardiac Death in Patients with Schizophrenia.

Characteristics	Schizophrenia Cohort *N* (%)	Sudden Cardiac Death *N* (%)	Adjusted Hazard Ratio[a]	95% CI	*P*	Population Attributable Fraction (%)
Total	170,322	1,836				
Physical illnesses						
Hypertension	23,101 (13.6)	661 (36.0)	1.38	1.23 to 1.55	<0.001	9.91
Ischemic heart disease	8,604 (5.1)	317 (17.3)	1.30	1.13 to 1.49	<0.001	3.98
Congestive heart failure	3,849 (2.3)	204 (11.1)	2.20	1.87 to 2.58	<0.001	6.06
Psychiatric illnesses						
Dementia and organic mental disorder	11,070 (6.5)	228 (12.4)	1.43	1.24 to 1.64	<0.001	3.73
Drug-induced mental disorder	6,414 (3.8)	86 (4.7)	2.22	1.78 to 2.77	<0.001	2.57

[a]Based on multivariate regression model in all of study subjects: the variables in Table 2 (demographics including sex, age, urbanization, employment) and the variables in Supplemental Table 1 (physical and psychiatric comorbidities) with $P < 0.001$ were remained in the final adjusted model.

Age Effect on Comorbidity Risk Factors for Sudden Cardiac Death in Patients with Schizophrenia

Considering that there was an age effect on the incidence and SMRs of sudden cardiac death in patients with schizophrenia (Table 1; Figure 1), stratified analyses were performed to assess the age effect on comorbidity risk factors for sudden cardiac death (Supplemental Tables 2, 3, and 4; organization of the tables were as per Table 4). Significantly, hypertension, congestive heart failure, and drug-induced mental disorder increased the risk of sudden cardiac death in patients with schizophrenia across the lifespan. In addition, chronic hepatic disease (2.38; 95% CI, 1.61 to 3.54; $P < 0.001$) and sleep disorder (1.77; 95% CI, 1.30 to 2.42; $P < 0.001$) raised the risk of sudden cardiac death among patients aged <35 years. Dementia and organic mental disorder (1.61; 95% CI, 1.26 to 2.05; $P < 0.001$) increased the risk of sudden cardiac death in patients aged between 35 and

Table 4. Cox Proportional Hazards Model of Physical and Psychiatric Comorbidity on the Risk of Sudden Cardiac Death in Patients with Schizophrenia, Stratified by Age Subgroups.

Characteristics	Schizophrenia Cohort ($N = 170,322$) *N* (%)	Sudden Cardiac Death ($n = 1,836$) *N* (%)	Adjusted Hazard Ratio	95% CI	P	Population Attributable Fraction (%)
Subgroup with age <35[a]	76,325	198				
Physical illnesses						
Hypertension	1,411 (1.9)	18 (9.1)	3.06	1.79 to 5.25	<0.001	6.12
Congestive heart failure	201 (0.3)	7 (3.5)	6.91	3.05 to 15.68	<0.001	3.03
Chronic hepatic disease	3,563 (4.7)	32 (16.2)	2.38	1.61 to 3.54	<0.001	9.37
Psychiatric illnesses						
Sleep disorder	15,638 (20.5)	62 (31.3)	1.77	1.30 to 2.42	<0.001	13.62
Drug-induced mental disorder	3,339 (4.4)	24 (12.1)	2.53	1.64 to 3.92	<0.001	7.33
Subgroup with age 35 to 54[b]	61,453	665				
Physical illnesses						
Hypertension	7,421 (12.1)	144 (21.7)	2.08	1.71 to 2.53	<0.001	11.24
Congestive heart failure	847 (1.4)	33 (5.0)	3.02	2.09 to 4.37	<.001	3.32
Psychiatric illnesses						
Dementia and organic mental disorder	4,018 (6.5)	75 (11.3)	1.61	1.26 to 2.05	<0.001	4.27
Drug-induced mental disorder	2,658 (4.3)	41 (6.2)	1.79	1.30 to 2.46	<0.001	2.72
Subgroup with Age ≥55[c]	32,544	973				
Physical illnesses						
Hypertension	14,239 (43.8)	499 (51.3)	1.31	1.14 to 1.50	<0.001	12.13
Ischemic heart disease	5,500 (16.9)	267 (27.4)	1.53	1.31 to 1.79	<0.001	9.51
Congestive heart failure	2,801 (8.6)	164 (16.9)	2.22	1.85 to 2.67	<0.001	9.27
Psychiatric illnesses						
Drug-induced mental disorder	417 (1.3)	21 (2.2)	2.25	1.45 to 3.48	<0.001	1.20

[a]Based on multivariate regression model in study subjects aged <35 years: sex, age, urbanization, employment, and the variables in Supplemental Table 2 (physical and psychiatric comorbidities) with $P < 0.001$ were remained in the final adjusted model.
[b]Based on multivariate regression model in study subjects aged between 35 and 54 years: sex, age, urbanization, employment, and the variables in Supplemental Table 3 (physical and psychiatric comorbidities) were with $P < 0.001$ remained in the final adjusted model.
[c]Based on multivariate regression model in study subjects aged ≥55 years: sex, age, urbanization, employment and the variables in Supplemental Table 4 (physical and psychiatric comorbidities) with $P < 0.001$ were remained in the final adjusted model.

54 years. Ischemic heart disease (1.53; 95% CI, 1.31 to 1.79; $P < 0.001$) elevated the risk of sudden cardiac death in patients aged ≥55 years.

As for the age effect on the PAF of the distinctive comorbidity for sudden cardiac death, sleep disorder had the highest PAF for sudden cardiac death (13.62%) in patients aged <35 years, followed by chronic hepatic disease (9.37%) and drug-induced mental disorder (7.33%). Among patients aged 35 to 54 years, hypertension had the highest PAF for sudden cardiac death (11.24%), followed by dementia and organic mental disorder (4.27%). In respect of patients aged ≥55 years, hypertension had the highest PAF for sudden cardiac death (12.13%), followed by ischemic heart disease (9.51%) and congestive heart failure (9.27%).

Discussion

To our knowledge, this is the first nationwide population-based cohort study to explore the age effect on the incidence and risk of the physical and psychiatric comorbidity for sudden cardiac death in patients with schizophrenia. We found that patients with schizophrenia had a 2.91-fold higher risk of sudden cardiac death relative to the general population. In addition, the SMRs in the schizophrenia cohort were >1.00 across all 3 age intervals and for both sexes, with the highest SMR in male patients aged <35 years (30.88; 95% CI, 26.18 to 36.18). Consistent with previous studies, [14,17] our findings from a Taiwanese national cohort suggest the urgency of formulating preventive strategies against sudden cardiac death in people with schizophrenia, particularly for younger male patients.

In this study, we determined a lower risk of sudden cardiac death among patients with schizophrenia who were employed or living in a highly urbanized area. Previous studies have shown that patients with schizophrenia are more likely to receive suboptimal medical care for their physical illnesses, which has resulted in excessive mortality.[29-34] Such suboptimal medical care is due to complex reasons, possibly related to patients' decreased ability for self-care and limited access to medical service.[35,36] Evidence has suggested that the association between risk of sudden cardiac death and residence in a rural area is related to the referral rate of specialist care.[37] In addition, higher neuropsychological abilities in patients with schizophrenia predict more favorable vocational outcomes.[38] Therefore, our finding of the decreased risk of sudden cardiac death in patients with

schizophrenia who were employed or living in a highly urbanized area may reflect their greater ability for self-care and utilization of medical services.

Crucially, our study demonstrated that hypertension, congestive heart failure, and drug-induced mental disorder were the major comorbidities increasing the risk of sudden cardiac death across the lifespan in patients with schizophrenia. These findings are consistent with studies that have demonstrated that both physical and psychiatric comorbidities increase the risk of sudden cardiac death in patients with schizophrenia.[14,17] Furthermore, according to our stratified analyses, the fractions of sudden cardiac death attributable to hypertension and congestive heart failure increased with age. Conversely, the fraction of sudden cardiac death attributable to drug-induced mental disorder decreased with age. In Taiwan, methamphetamine is one of major classes of illicit drugs.[39] Our previous study revealed that methamphetamine increases the risk of arrhythmia particularly in younger patients,[40] which may partly explain the observed association between sudden cardiac death and drug-induced mental disorder in young patients with schizophrenia. Taken together, the findings from our prospective national cohort study suggest that, in contrast to psychiatric comorbidities, physical comorbidities, especially cardiovascular diseases, contribute more to sudden cardiac death among older adult patients with schizophrenia.

In addition to hypertension, congestive heart failure, and drug-induced mental disorder, we noted that chronic hepatic disease and sleep disorder increased the risk of sudden cardiac death in patients with schizophrenia aged <35 years. The reasons underlying these associations remain unknown but can be plausible.

To conjecture, systemic inflammation is a potential mechanism. Studies have demonstrated that patients with schizophrenia are characterized by inflammation-promoting risk genes.[41,42] Additionally, patients with chronic hepatic disease or sleep disorder have been observed to have increased levels of inflammatory markers such as interleukin-6 and highly sensitive C-reactive protein.[43,44] Interleukin-6 and highly sensitive C-reactive protein can impair calcium regulation in cardiomyocytes, causing QTc prolongation and arrhythmia[45,46]; thus, patients with schizophrenia and comorbid chronic hepatic disease and sleep disorder may exhibit increased risks of sudden cardiac death. Moreover, studies have demonstrated that patients with schizophrenia have increased risks of body weight gain and obesity in their early adulthood.[47] In addition, obesity elevates the risk of numerous physical disorders, including cardiovascular diseases, nonalcoholic fatty liver disease, and obstructive sleep apnea.[48,49] Given that we did not specifically investigate obstructive sleep apnea in this study, further research must be conducted to determine whether obesity is a common factor linking nonalcoholic fatty liver disease, obstructive sleep apnea, and sudden cardiac death in young adult patients with schizophrenia.

Among patients with schizophrenia aged between 35 and 54 years, we identified dementia and organic mental disorder to collectively be an additional risk factor for sudden cardiac death. A recent nationwide population-based cohort study from Denmark determined a 2-fold higher risk of dementia among patients with schizophrenia.[6] Furthermore, a recent meta-analysis discovered that patients with schizophrenia who were younger than 65 years had a comparable relative risk of dementia to individuals aged 65 years and older.[50] Moreover, patients with schizophrenia and cognitive deficits may have decreased self-care ability, thus worsening physical health and causing, for example, hypertension and congestive heart failure,[35,36,51] our study's findings suggest that clinicians must begin assessing the cognitive function and cardiovascular health of patients with schizophrenia before they enter into older age (at 55 years).

Limitations

Our study has several limitations. First, the diagnoses of schizophrenia and comorbidities in this study were based on only the ICD codes in NHIRD claims data. Nevertheless, the NHI Administration conducts yearly randomized reviews of the NHIRD by using medical records to verify the diagnoses therein. Therefore, the NHIRD is of acceptable accuracy with respect to the coding for epidemiological analysis. Second, laboratory test data could not be obtained from the NHIRD. These data can provide insights into the pathogenesis mechanisms of sudden cardiac death associated with schizophrenia. Third, due to the limitation inherent to the use of the NHIRD, data related to obesity-related measures (e.g., body mass index and waist circumference) and lifestyle variables (e.g., smoking and diet habits) were not available in the present analyses. Fourth, given that sudden cardiac death related to antipsychotic medication is usually attributed to arrhythmia and myocarditis, our present study design may not have been suitable for assessing the acute exposure effect of antipsychotic medications on the risk of sudden cardiac death. Future research with a case-crossover design is necessary to explore this crucial topic.

Conclusions

This prospective nationwide population-based cohort study noted a high risk of sudden cardiac death in patients with schizophrenia across the lifespan. Particularly, the SMR of sudden cardiac death is the highest among male patients aged <35 years. Furthermore, different comorbidities have distinctive age-dependent risks of sudden cardiac death. Given the facts that patients with schizophrenia are at an increased risk of excessive cardiac mortality, prevention strategies that account for the age effect are urgently required.

Authors' Note

Drs. PH Chen, Chang, and Kuo led the conception and design of the study. Dr. Kuo acquired the data, and Mr. Su performed the statistical analysis. Drs. PH Chen and Kuo wrote and revised the manuscript. Drs. Pan and YL Chen made critical and substantive revisions to the manuscript. Drs. Tsai and CC Chen supervised the study. Please use the following website: http://nhird.nhri.org.tw/en/ to request information on the database this study used, such as the point of contact, data protection, and content of data files. The database is composed of medical claim files representative of the entire population in Taiwan.

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Supplemental Material

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