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Original article

Increased risk of dementia in patients with Schizophrenia: A population-based cohort study in Taiwan

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ABSTRACT

Background: The extent to which schizophrenia is associated with the risk of all-cause dementia is controversial. This study investigated the risk of dementia by type in patients with schizophrenia.
Methods: Data were collected from the Taiwanese National Health Insurance Database 2005 and analyzed using multivariate Cox proportional hazard regression models to determine the effect of schizophrenia on the dementia risk after adjusting for demographic characteristics, comorbidities, and medications. Fine and Gray's competing risk analysis was used to determine the risk of dementia, as death can act as a competing risk factor for dementia.
Results: We assessed 6040 schizophrenia patients and 24,160 propensity scale-matched control patients. Schizophrenia patients exhibited a 1.80-fold risk of dementia compared to controls (adjusted hazard ratio [aHR] = 1.80, 95% confidence interval [CI] = 1.36 ~ 2.21, $p < 0.001$) after adjusting for covariates. Cardiovascular disease (aHR = 5.26; 95% CI = 4.50 ~ 6.72; $p < 0.001$), hypertension (aHR = 1.83; 95% CI = 1.77 ~ 2.04; $p = 0.002$), traumatic head injury (aHR = 1.35; 95% CI = 1.24 ~ 1.78; $p < 0.001$), chronic lung diseases (aHR = 1.64; 95% CI = 1.13 ~ 2.56; $p < 0.001$), alcohol-related disorders (aHR = 3.67; 95% CI = 2.68 ~ 4.92; $p < 0.001$), and Parkinson's disease (aHR = 1.72; 95% CI = 1.25 ~ 2.40; $p < 0.001$) were significantly associated with dementia risk. Notably, first-generation antipsychotics (aHR = 0.80; 95% CI = 0.56 ~ 0.95; $p = 0.044$) and second-generation antipsychotics (aHR = 0.24; 95% CI = 0.11 ~ 0.60; $p < 0.001$) were associated with a lower dementia risk. Sensitivity tests yielded consistent findings after excluding the first year and first 3 years of observation. Patients with schizophrenia had the highest risk of developing Alzheimer's [dementia/disease?] among dementia subtypes (aHR = 2.10; 95% CI = 1.88 ~ 3.86; $p < 0.001$), followed by vascular dementia (aHR = 1.67; 95% CI = 1.27 ~ 2.12; $p < 0.001$) and unspecified dementia (aHR = 1.30; 95% CI = 1.04 ~ 2.01; $p < 0.001$).
Conclusions: Schizophrenia was significantly associated with the risk of all-cause dementia. Data are scarce on the mechanisms through which antipsychotic agents protect persons with schizophrenia from developing dementia. Further research is recommended to elucidate the neurobiological mechanisms underlying the association between schizophrenia and dementia, and whether antipsychotics protect against the development of dementia in schizophrenia.
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1. Introduction

Dementia is a clinical syndrome characterized by cognitive decline and impairment in activities of daily living [1]. Although the etiology is not well known, risk factors of dementia have been studied to determine the basic mechanisms leading to dementia. Prior studies on the risk factors of dementia mainly focused on Alzheimer's dementia, as it is the most common type of dementia.

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An older age [2,3], cardiovascular risk factors (smoking, hypertension, diabetes mellitus, and heart disease) [4], and genetic factors [5] are well-known risk factors of dementia. By influencing these risk factors, it is hoped that clinicians can modify the course of the disease.

Schizophrenia, affecting approximately 1% of the population, is associated with disturbances in perception, communication, and thought processes as well as abnormalities in behavior [6,7]. Schizophrenia is also characterized by cognitive impairment [8]. Robust evidence of impairment was reported across a multitude of cognitive domains, including current IQ, category fluency, verbal memory, abstract thinking, language, sustained attention, response inhibition, and symbol coding tasks [9–11]. Nevertheless, the association between schizophrenia and the risk of subsequent dementia remains unclear. Studies of the relationship between schizophrenia and dementia are few, and their results are inconsistent. Several studies reported cognitive impairment or even dementia in patients with schizophrenia [12–14]. However, one cross-sectional study revealed no evidence of accelerated decline in cognitive abilities in schizophrenics compared to five age-derived cohorts [15]. Discrepancies among those studies may be due to short follow-up periods, small sample sizes [16,17], and the selection of chronically institutionalized older patients [16,18,19]; these issues reduce the validity of research on dementia risk and schizophrenia. Despite one recent nationwide Danish cohort study with a sufficient size and follow-up time revealing a strong association between schizophrenia and dementia risk [20], it lacked adjustment for medication effects on the dementia risk for patients with schizophrenia. In addition, most aforementioned studies did not adjust for dementia-related risk factors, and whether there is an interaction between schizophrenia and several covariates and their association with dementia were not thoroughly investigated. Moreover, most of those studies were conducted in western countries, and whether such findings would be observed in Asian populations remains unknown. Therefore, we conducted a more-comprehensive assessment to evaluate the risk of dementia in schizophrenia using the Taiwan National Health Insurance (NHI) Research Database (NHIRD). We hypothesized that schizophrenia would be associated with an increased risk of subsequent dementia in later life.

2. Methods

2.1. Database

Taiwan's NHI was established in 1995, and nearly 99% of residents are enrolled in this database [21]. This study used the Longitudinal Health Insurance Database 2005 derived from Taiwan's NHIRD. These data include registration and medical claims for 1,000,000 randomly sampled individuals from the total 25.68 million beneficiaries registered in the NHIRD in 2005. The database includes detailed information regarding the health insurance system between 2000 and 2013. Patient consent was not required to access the NHIRD as data were analyzed anonymously. Although the study was entirely based on register data, ethical permission was still required according to Taiwanese law. This study was exempted from ethical approval by the Institutional Review Board of Taipei Tzu Chi Hospital (IRB no.: 04-X36-094).

2.2. Inclusion criteria for patients with Schizophrenia and the control cohort

Since Taiwan's NHI was launched in 1995, patient's medical claims before 1995 are unavailable. Therefore, information with regard to patients diagnosed with schizophrenia before 1995 was not available, and thus the duration of illness could not be determined. Therefore, we chose new-onset schizophrenia patients as our study cohort to prevent survival bias. Finally, patients diagnosed as having new-onset schizophrenia (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] 295) between January 1, 2000, and December 31, 2013, were included in the schizophrenia cohort ($n = 9243$). To recruit only patients who were first diagnosed with schizophrenia, we excluded patients with a previous diagnosis of schizophrenia before 2000 ($n = 2771$). The enrollment date was considered the index date. We also excluded patients with a previous history of dementia (ICD-9-CM 290, 294.1 ~ 294.2, and 331) that was diagnosed before the first diagnosis of schizophrenia ($n = 231$), those of unspecified sex ($n = 16$), and those younger than 18 years ($n = 185$). The final schizophrenia cohort consisted of 6040 patients with newly diagnosed schizophrenia.

Our control cohort was selected from the remaining patients during the same period (January 1, 2000 to December 31, 2013). Using similar exclusion criteria as in the study cohort, patients with any diagnosis of schizophrenia before 2000 ($n = 2118$) and patients who had been diagnosed with any mental disorder ($n = 5082$; ICD-9-CM 290 ~ 319) were also excluded to ensure that no psychiatric patients were included in the control group. We further excluded patients who had previously been diagnosed with dementia ($n = 207$). Patients on antipsychotic medications ($n = 621$) were excluded from the control cohort to ensure that no one with a psychotic disorder was included. Similarly, patients of an unspecified sex ($n = 27$) or younger than 18 years ($n = 176{,}442$) were also excluded. From the remaining eligible subjects, we selected a control cohort that contained four times the number of patients with schizophrenia, propensity score-matched by sex, age, and index year [22]. The first time the patient in the control cohort sought medical consultation during 2000 ~ 2013 was considered the index date. Schizophrenia and dementia must have been diagnosed at least twice for consecutive outpatients or once for inpatient medical records for validation. The reason for the requirement for two consecutive diagnoses from outpatient medical records was to minimize the possibility of recruiting patients who were erroneously coded in a single outpatient visit. Discharge diagnoses are highly reliable; therefore, a single record was sufficient. Finally, our study included 24,160 control patients. A flow chart of the study selection process is provided in Fig. 1.

2.3. Study endpoint and covariates

The date of any form of dementia diagnosis (ICD-9-CM 290, 294.1 ~ 294.2, and 331) made for the first time during the follow-up (from enrollment to December 31, 2013) or the end of the study (December 31, 2013) was considered the study endpoint. In our study, types of dementia other than Alzheimer's and vascular dementia were categorized as unspecified dementia, such as frontotemporal dementia (FTD), Parkinson's dementia, and dementia with Lewy body (DLB) or dementia of unknown etiology. Sociodemographic variables consisted of sex, age, income-related insurance premium, hospital type, season, and urbanization level. Potential baseline dementia-related clinical factors were also assessed as medical comorbidities, including cardiovascular disease (ICD-9-CM 430 ~ 438), hypertension (ICD-9-CM 401 ~ 405), diabetes mellitus (ICD-9-CM 250), hypercholesterolemia (ICD-9-CM 272), chronic respiratory disease (ICD-9-CM 491 ~ 494, 496, 415.0, 416.8, and 416.9), traumatic brain injury (ICD-9-CM 800 ~ 804, 850 ~ 854, and 959), alcohol-related disorders (ICD-9-CM 291, 303, 305.0, 357.5, 425.5, 535.3, 571.0, and 571.1 ~ 571.3), and Parkinson's disease (ICD-9-CM 332) 1 year before enrollment [23–47]. Medications in medical claims during the entire follow-up period considered in the analysis were

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