Article

Schizophrenia and Hospital Admissions for Cardiovascular Events in a Large Population: The APNA Study

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Abstract: (1) Background: Patients with schizophrenia have higher mortality, with cardiovascular diseases being the first cause of mortality. This study aims to estimate the excess risk of hospital admission for cardiovascular events in schizophrenic patients, adjusting for comorbidity and risk factors. (2) Methods: The APNA study is a dynamic prospective cohort of all residents in Navarra, Spain. A total of 505,889 people over 18 years old were followed for five years. The endpoint was hospital admissions for a cardiovascular event. Direct Acyclic Graphs (DAG) and Cox regression were used. (3) Results: Schizophrenic patients had a Hazard Ratio (HR) of 1.414 (95% CI 1.031–1.938) of hospital admission for a cardiovascular event after adjusting for age, sex, hypertension, type 2 diabetes, dyslipidemia, smoking, low income, obesity, antecedents of cardiovascular disease, and smoking. In non-adherent to antipsychotic treatment schizophrenia patients, the HR was 2.232 (95% CI 1.267–3.933). (4) Conclusions: Patients with schizophrenia have a higher risk of hospital admission for cardiovascular events than persons with the same risk factors without schizophrenia. Primary care nursing interventions should monitor these patients and reduce cardiovascular risk factors.

Keywords: cardiovascular; schizophrenia; prospective cohort; hospital admissions

1. Introduction

Schizophrenia is a severe mental illness associated with elevated cardiovascular disease risk. Patients with schizophrenia have higher comorbidity (notably higher risk of cardiovascular diseases) and higher mortality [1]. A meta-analysis showed that mortality rates were 2.5 times higher in patients with schizophrenia. Suicides were higher in patients with schizophrenia. In addition, mortality rates from the major causes of death were higher in patients with schizophrenia than in the general population [2]. Cardiovascular disease is the first leading cause of mortality in patients with schizophrenia, followed by cancer and suicide [3,4].

Likewise, the onset of the first episode of vascular diseases is lower [5]. Moreover, revascularization rates are lower after an infarction in patients with schizophrenia [6]. A cohort study conducted in Singapore showed that patients with schizophrenia with physical comorbidity (diabetes, hypertension, coronary heart disease, and cancer) had an increased mortality risk [7]. A problem in patients with schizophrenia is non-adherence to treatment

with antipsychotic drugs, which can reach 42% [8]. However, this figure could be even higher because a clinical trial found 74% of patients discontinued antipsychotic treatment after 1.5 years [9]. This non-adherence could affect lifestyle and affect the appearance of cardiovascular diseases [10–13].

This research aims to study whether patients with schizophrenia have an increased risk of hospital admissions for cardiovascular diseases independently of their comorbidity.

2. Materials and Methods

The "Navarre primary health care system cohort" (APNA study) is a dynamical multipurpose prospective cohort. It started in 2004 in the autonomous community of Navarre (northern Spain). Details on the cohort design are available elsewhere [14–19].

Briefly, the population of Navarra primary health care data has been recorded since 2004 [17]. In this study, we selected people over 18 years old. The follow-up in this study was from 2012 to 2016. The average population in the period was 505,889 people.

2.1. Study Variables

We collected age, sex, date of hospital admissions for cardiovascular events, and income status. Income levels were obtained from the TSI used for the pharmaceutical co-payment. TSI 001 code which includes people with non-contributory pensions (5150 EUR/year), Social Integration Income (7640 EUR/year), or unemployed people without unemployment benefits, was considered low income [20]. We obtained from the Navarra hospital discharge registration system the date of the first hospital admission with a cardiovascular event (CVE) as the main reason for admission during the follow-up period. We considered CVE those hospital admissions with a diagnosis codified as a cerebrovascular disease with the International Classification of Diseases 10th version (ICD10) codes 430–438; ICD10: I60–I69) or ischemic heart (ICD10: 410–414; ICD10: I20–I25). We consider as an antecedent of CVE a hospital admission with a diagnosis codified as cerebrovascular disease or ischemic heart disease before 2012. We followed patients until an event occurred or until 31 December 2016.

Clinical variables: the following variables were used: weight (kilograms), height (meters), Body Mass Index (BMI) (weight/height^2), systolic and diastolic BP (mmHg), and smoking during the follow-up period. Patients with BMI $\geq$ 30 were classified as obese. We recorded diagnoses of type 2 diabetes, hypertension, and dyslipidemia. We extracted the antecedents of previous hospital admission for cardiovascular events from hospital records. We used the same codes mentioned above. Comorbidity was computed with the Charlson Index [21] and the Comorbidity Index [22].

Patients with schizophrenia diagnosis using ICD10 by a psychiatrist from Navarre Health Service were identified in the database. A person who had not been diagnosed with schizophrenia was considered free from the illness.

The number of bottles of antipsychotic medication purchased at each pharmacy by each patient was extracted from the drug prescription database. A patient was considered non-adherent to antipsychotic treatment when they had not purchased antipsychotic medication from the pharmacy for one year. The definition of non-adherence to antipsychotic treatment is much debated [23,24]. In general, non-adherence to antipsychotic treatment exists when patients stop taking between 20% and 30% of the medication [23,24]. In our case, we did not have monthly figures and only annual figures, so it was difficult to know if a patient had stopped taking the medication since there could be two scenarios: a patient could change medication or take several medications simultaneously. For this reason, we chose one year without any medication as the criterion for non-adherence.

2.2. Statistical Analysis

Although it is helpful for simple causal structures, the traditional approach to confounding is inadequate for more complex causal networks. Adjustments for many variables can open back paths and introduce bias [25]. For these reasons, many editors agreed in a

document entitled "Guidelines for the Control of Confounding and Reporting of Results in Causal Inference Studies" [25].

A valuable tool for this purpose is DAGs (Directed Acyclic Graph). DAGs allow drawing a theoretical map of the relationships among variables determining what variables should be controlled in a multivariate model, avoiding bias [26]. In a DAG, unidirectional arrows represent known causal effects (based on the existing knowledge). DAG allows determining what variables should be controlled as cofounders. The determination of the variables to be controlled can be done manually or using software such as Daggity [27].

We used DAG (Figure 1) to study the relationship of schizophrenia with hospital admissions for cardiovascular events and potential confounding factors. The DAG graphics indicates that sex influences dyslipidemia, type 2 diabetes, smoking, Charlson Index, hypertension obesity, antecedents of cardiovascular events, schizophrenia, and hospital admissions for cardiovascular events. Using this graph, the software Dagitty indicated that the possible cofounders that should be adjusted were age, antecedents cardiovascular diseases, comorbidity (Charlson Index), dyslipidemia, hypertension, income, obesity, sex, smoking, and type 2 diabetes. Supplementary Figure S1 shows the causal path between schizophrenia and hospital admissions for cardiovascular events.
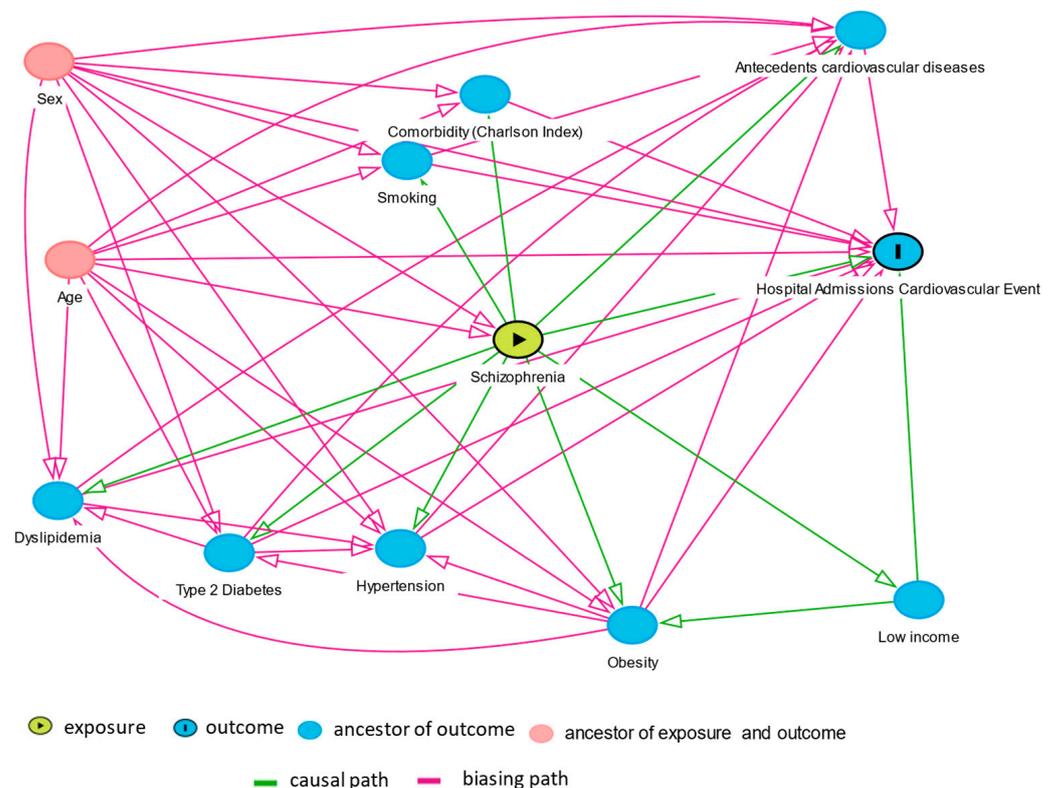

Figure 1. Directed Acyclic Graph (DAG) of schizophrenia and hospital admissions for cardiovascular events.

In the descriptive analysis, we present the data of categorical variables as proportion with confidence intervals. When adequate, we give mean and standard deviation or median and interquartile deviation in the quantitative variables. Comparisons among categorical variables were calculated with the Chi-square test. Comparisons between groups in quantitative variables were performed with Student's *t*-test. When quantitative variables were scales or had no normal distribution, the Kruskal–Wallis test was performed.

Multivariate analysis was performed in two steps. First, a DAG was drawn. Daggity software identified the variables to be adjusted. In the second step, the multivariate models were made adjusting for those variables identified as cofounders in the DAG. Cox regression was used to estimate the excess risk of hospital admissions for cardiovascular events associated with schizophrenia. In the Cox models, adjustment was made for all variables identified by as confounding factors in the DAG. There was a high correlation between Charlson and the Comorbidity Index. As a result, we used the Charlson Index in the analysis. Data were analyzed with IBM SPSS and Openepi [28].

3. Results

The analysis included 505,889 people with 2,700,505 follow-up years. During the following period, there were 8639 vascular events. The incidence of cardiovascular events was 355.5 per 100,000 person-years in patients with schizophrenia versus 91.1 per 100,000 person-years in persons without schizophrenia with a Rate Ratio of 3.903 (95% CI 2.924–5.208). The proportion of males was higher in persons with schizophrenia, 59.8%, than in persons without schizophrenia, 49.2% (Table 1). The proportion of persons with low income was four times higher in patients with schizophrenia, 12.9% vs. 3.8%. Obesity, diabetes, and smoking were higher in patients with schizophrenia, while the prevalence of hypertension was lower than in persons without the disease. Dyslipidemia, comorbidity, and Charlson Index were similar in both groups.

Table 1. Patients' characteristics.

Variables	Schizophrenia N = 2495 % Mean (SD)	No Schizophrenia N = 503,394 % Mean (SD)	*p*
Age (years)	49.7 (15.7)	50.0 (18.0)	0.342 [†]
Male	59.8%	49.2%	<0.001 [‡]
Low income	12.9%	3.8%	<0.001 [‡]
Charlson Index	1.3 (1.8)	1.3 (1.7)	0.677 [*]
Comorbidity Index	1.2 (1.5)	1.2 (1.7)	0.512 [*]
(Obesity) BMI $\geq$ 30	41.5%	25.9%	<0.001 [‡]
BMI	29.4 (6.3)	27.2 (5.2)	<0.001 [†]
CV antecedents	8.9%	9.5%	0.243 [‡]
Diabetes	7.8%	5.4%	<0.001 [‡]
Hypertension	12.5%	15.1%	0.001 [‡]
Dyslipidemia	27.1%	25.9%	0.221 [‡]
Smoking	19.8%	9.1%	<0.001 [‡]

[†] Student's T; [‡] Chi-square; [*] Kruskal–Wallis; SD = standard deviation; BMI = Body Mass Index; CV = cardiovascular.

There were 2495 patients with schizophrenia. Patients with schizophrenia had been diagnosed for an average of 15.82 years. (95% CI 14.19–17.45). Of these patients, 9.5% had antecedents of cardiovascular events.

The more common treatment was Oxazepine and Thiazepine, with 39.5% of the patients taking the medication, followed by Risperidone 19.3% and Olanzepine with 18.1% (Table 2).

Table 2. Distribution of patient antipsychotic medication.

Medications	N	% *
Oxazepine and thiazepine	984	39.5
Risperidone	482	19.3
Olanzepine	451	18.1
Clozapine	264	10.6
Quetiapine	238	9.5
Clotiapine	128	5.1
Asenapine	8	0.3

* The percentages add up to more than 100% because patients may take two drugs or change medications.

A moderate percentage of patients with schizophrenia, 27.77% (95% CI 26.04–29.56), were non-adherent to antipsychotic treatment, i.e., they had not withdrawn their prescription medication from the pharmacy for at least one year.

The Charlson Index was not included in the models because of collinearity with age. The models with the Charlson Index are presented in the supplementary material (Tables S1 and S2). The results are very similar to those without the Charlson Index presented in the article.

On the Cox model adjusted for age and sex, patients with schizophrenia compared with people without schizophrenia had a Hazard Ratio (HR) of 1.348 (1.009–1.801) for a cardiovascular event hospital admission, $p = 0.044$ (Table 3). In the final multivariate model adjusted for age, sex, hypertension, type 2 diabetes, dyslipidemia, income, obesity, antecedents of cardiovascular disease, and smoking, patients with schizophrenia had an HR of 1.421 (95% CI 1.037–1.948).

Table 3. Cox regression for hospital admission for cardiovascular events in patients with schizophrenia.

Variables	Model Adjusted by Age and Sex		Model Adjusted *	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Schizophrenia	1.348 (1.009–1.801)	0.044	1.421 (1.037–1.948)	0.029

HR = Hazard Ratio; * adjusted by hypertension, age, sex, type 2 diabetes, dyslipidemia, cardiovascular antecedents, smoking, income, and obesity (BMI $\geq$ 30).

Patients with schizophrenia who have stopped treatment had an HR adjusted by age and sex of 1.778 (95% CI 1.071–2.951). There were no differences in the risk between patients with schizophrenia following antipsychotic treatment and those without schizophrenia (Table 4).

The final multivariate model was adjusted for age, sex, hypertension, type 2 diabetes, dyslipidemia, smoking, low income, obesity, antecedents of cardiovascular events, and smoking. Patients with schizophrenia without treatment had an HR of 2.232 (95% CI 1.267–3.933). The most significant risk factor for developing a cardiovascular event was having had another cardiovascular event that required hospitalization prior to the follow-up period, with an HR of 6.559, followed by non-adherence to antipsychotic treatment with an HR of 2.232, followed by male sex with an HR of 1.953, type 2 diabetes with an HR of 1.531, and low income with 1.494. In conclusion, we can state that non-adherence to antipsychotic treatment increases the risk of having a cardiovascular event that requires hospitalization by 123%.

Table 4. Cox regression for hospital admission for cardiovascular events according to schizophrenia treatment.

Variables	Model Adjusted by Age and Sex		Full Model Adjusted *	
	HR (95% CI)	p	HR (95% CI)	p
No schizophrenia	1	-	1	-
Treated schizophrenia	1.206 (0.848–1.717)	0.297	1.224 (0.838–1.267)	0.296
Non-adherence to antipsychotic treatment	1.778 (1.071–2.951)	0.026	2.232 (1.267–3.933)	0.005
Age	1.077 (1.076–1.079)	<0.001	1.044 (1.042–1.046))	<0.001
Sex (male)	2.465 (2.355–2.580)	<0.001	1.953 (1.857–2.054)	<0.001
High blood pressure	-	-	1.143 (1.076–1.189)	<0.001
Type 2 diabetes	-	-	1.531 (1.451–1.615)	<0.001
Antecedents CVE	-	-	6.559 (6.218–6.919)	<0.001
Smoking	-	-	1.134 (1.046–1.230)	0.002
Low income	-	-	1.494 (1.307–1.709)	<0.001
Dyslipidemia diagnosis or total cholesterol > 250 mg/dL	-	-	1.080 (1.030–1.132)	0.001
Obesity BMI ≥ 30	-	-	1.145 (1.090–1.203)	<0.001

HR = Hazard Ratio; CVE = cardiovascular event; BMI = Body Mass Index; * adjusted by all the variables in the model.

4. Discussion

This study shows that people with schizophrenia have a higher probability of cardiovascular events. This association remains after adjusting for sociodemographic factors and comorbidity. Individuals with severe mental illness experience increased morbidity and mortality compared to the general population. Among the explanations could be a higher prevalence of hazardous health behaviors that are cardiovascular risk factors (smoking, addiction, poor diet, lack of exercise, obesity) [29]. Molecular and genetic mechanisms [30], such as an accelerated shortening of the telomeres, may also play a role [31].

It is also possible that there may be differences in the accessibility of health care, the detection of somatic diseases, their treatment, and the attitudes of health care professionals [32]. A metanalysis found that patients with schizophrenia have less screening and lower-quality treatment [33]. Thus, a retrospective cohort study conducted in Ontario showed that patients with schizophrenia were less frequently treated with thrombolysis. These patients had fewer diagnostic tests, such as carotid imaging. They were less likely to be in rehabilitation or treated with anticoagulants, antihypertensives, or lipid-lowering drugs at discharge [34].

The cardio-metabolic adverse effects of antipsychotics, including weight gain, may contribute to the development of metabolic syndrome [3,35,36], which is associated with an increased risk of all-cause and cardiovascular disease mortality. Antipsychotic drugs may exacerbate atherosclerosis [37]. Dysregulation of coagulation and complement may occur in patients with schizophrenia under treatment [38]. However, we found that patients who had discontinued antipsychotic treatment had a higher risk of cardiovascular events.

Patients with schizophrenia with diabetes have a higher risk of mortality and cardiovascular disease than persons without schizophrenia with diabetes [39]. Although the mechanisms leading to increased morbidity from cardiovascular disease are not yet precise, clinicians, especially general practitioners (GPs) dealing with patients with schizophrenia, should be aware that they have an increased likelihood of cardiovascular disease. In this research, we adjusted for the factors influencing CVE. The increased CV risk may be due to

factors that have not been assessed for the degree of control of these risk factors, such as diabetes, hypertension, and dyslipidemia. Our investigation has adjusted for being diabetic or not, but not for being well or poorly controlled for diabetes. Future research should study differences in the control of cardiovascular risk factors.

Nurses' intervention programs have been shown to reduce cardiovascular risk factors in women with schizophrenia [40]. Clinical trials are currently underway to reduce cardiovascular risk in young patients with schizophrenia [41]. Nurses' health promotion programs should be carried out in patients with schizophrenia to reduce cardiovascular risk factors [42]. Another issue we detected is that patients who do not follow the treatment have a higher risk of developing a cardiovascular event. The explanation could be because they changed their lifestyle to a higher-risk lifestyle. In any case, another intervention of the community nurse would be to follow up with these patients to ensure that they take their medication.

In this study, the main limitation is that we only had access to hospital admissions. We did not have access to death certificates, so the incidence rate is probably underestimated and higher than the estimates presented. Another limitation is that we did not analyze the physical exercise of the patients since this is an item that is usually poorly recorded in the computerized medical records. One limitation is that the medication information we handle only tells us that the antipsychotic medication was purchased by the patient or the patient's family, but we do not know whether the patient was taking the medication. Our study provides lower figures for non-adherence to antipsychotic treatment than those of the literature because our criterion was very stringent: one year without picking up the medication from the pharmacy, which could lead to underestimating non-adherence to antipsychotic treatment. The figures in the literature are slightly higher than ours. A meta-analysis found around 42% non-adherence to antipsychotic treatment compared to the figure we found of 27.77% [8]. However, it is more likely that lifestyle changes affect CVE when the period without medication is more than one year versus three months in the most common definitions.

5. Conclusions

Schizophrenia patients have a higher risk of hospital admission for cardiovascular events than persons with the same risk factors without schizophrenia. Specialist physicians and general practitioners need to be aware of this increased cardiovascular risk in patients with schizophrenia and instruct nurses to monitor them and include them in their follow-up programs. Primary care nursing interventions should monitor these patients and reduce cardiovascular risk factors.

Informed Consent Statement: The database is an administrative database of Primary Health Care Clinical Records collected during routine procedures. All Primary Health Care Centers users knew that their clinical records were registered. They had the right to the cancellation of their records.

Data Availability Statement: The datasets generated for this study are unavailable due to the data protection law.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the study's design, in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

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