Prevalence of Cardiovascular Disease and Comorbid Risk Factors in Patients in Puerto Rico with Schizophrenia

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Objective: The mortality rate of schizophrenia patients is higher than that of the general population; cardiovascular disease (CVD) is their leading cause of death. This issue must be studied since people with schizophrenia are disproportionately burdened with CVD. Therefore, our goal was to identify the prevalence of CVD and other comorbidities, stratified by age and gender, in patients with schizophrenia living in Puerto Rico.

Methods: A retrospective, case-control, descriptive study was conducted. Subjects in this study were admitted to Dr. Federico Trilla's hospital from 2004 through 2014 for both psychiatric- and non-psychiatric conditions. The sample populations were stratified by the confounding variables of tobacco use and alcohol abuse, and the resulting stratification was analyzed with the Cochran–Mantel–Haenszel method.

Results: A higher frequency of CVDs was noted in the patients with schizophrenia compared to those in the control group. Although hypertension was the most frequent pathology encountered in both groups, ischemic heart disease was approximately four times more frequent in the patients with schizophrenia. CVD represented 58.4% and 52.7% in the schizophrenia and non-schizophrenia groups, respectively, although a statistically significant difference was not observed. The prevalence of malignancies in patients without schizophrenia was higher than in patients with schizophrenia. Moreover, the prevalence of asthma was 10.9% in the control group compared to 5.3% in the schizophrenia group.

Conclusion: These findings should motivate a systematic approach to prioritizing the aggressive management, early diagnosis, and prevention of comorbid risk factors in patients with schizophrenia. [*P R Health Sci J 2023;42(1):3-9*]

Key words: Schizophrenia, Comorbidities, Cardiovascular diseases, Prevalence, Puerto Rico

There is substantial comorbidity between chronic medical illnesses, such as hypertension, and severe mental illnesses, such as schizophrenia (1). More than 50% of patients with schizophrenia have 1 or more comorbid psychiatric or medical conditions (2). Moreover, the incidences of a wide range of diseases, such as diabetes mellitus (DM), obesity, metabolic syndrome, coronary heart diseases, and chronic obstructive pulmonary disease (COPD), are significantly higher in patients with schizophrenia than in the overall population (1).

Schizophrenia is a serious and persistent mental illness that is associated with a great societal financial impact (3). Follow-up studies of patients with schizophrenia have shown high rates of hospital readmission, high rates of unemployment, and overall poor long-term outcomes (4). Patients with schizophrenia also have increased mortality compared to the general population (1), which is mainly due to causal factors that are related to such lifestyle issues as poor diet, lack of physical activity, smoking, and substance abuse (5,6).

The most common natural cause of death is cardiovascular disease (CVD) (7), which is often the result of health problems associated with 'patients' psychiatric disorders, those problems including, but not being limited to, obesity, metabolic syndrome, and DM. Cardiovascular disease comprises disorders of the heart and blood vessels that include coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, and deep vein thrombosis and pulmonary embolism (8). The aforementioned entities occur more often and have worse outcomes in patients with

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serious mental illness than they do in the general population because of a combination of factors that include inadequate access to quality care, poor diet, lack of physical activity, smoking, and weight gain (which is associated with some antipsychotic medications) (9).

The prevalence rate for schizophrenia in adults that reside in Puerto Rico (PR) is 1.9% for males and 1.2% for females (10). To date, no studies have been conducted to establish the prevalence of CVD in patients with schizophrenia living in PR.

Given the morbidity and mortality rates of CVD in people living with schizophrenia, we deemed it crucial to study this issue, locally. Our goal was to identify effective treatment strategies aimed at the primary prevention of unfavorable risk factors in this vulnerable population. We hypothesized that participants with a clinical diagnosis of schizophrenia would have higher prevalences of various comorbidities, particularly CVD, compared to those prevalences in a population without a diagnosis of schizophrenia. This study aimed to identify, by age and gender, the prevalences of different comorbid conditions in patients with schizophrenia living in PR.

Patients and Methods

Study design

In order to characterize the prevalences of the different comorbid conditions and CVD in a sample of patients with schizophrenia in PR, we conducted a retrospective, case-control, descriptive study. All the patients recruited in this study were admitted to the University of PR "Dr. Federico Trilla" Hospital (UPRH), which is located in the municipality of Carolina, PR, for both psychiatric and non-psychiatric pathologies.

Study population

The specific populations under study were patients with a diagnosis of schizophrenia (at admission and/or at discharge) and patients admitted through the emergency department (ED) and diagnosed with a non-mental pathology. These populations represented our case-study and control groups, respectively.

Sample framework

We performed a 10-year (January 2004–December 2014) prevalence analysis, in which the medical records of patients with a diagnosis of schizophrenia and patients admitted through the ED but without said diagnosis were obtained for statistical comparison.

Sample size and selection

According to the most recent data obtained from the Centers for Disease Control, Hispanics have a 30% prevalence of CVD (11). In comparison, patients with schizophrenia have an estimated 40 to 50% prevalence of CVD (5). Based on this information and in accordance with our investigational model, a sample size of 103 was the minimum required for both the control and the study groups. This value was based on a 95% CI and a power of 80% to detect a statistically significant difference between the 30% and 50% prevalences of CVD in the study groups.

Inclusion and exclusion criteria

The inclusion criteria for our study group were patients admitted to the UPRH from January 2004 through December 2014 with a diagnosis of schizophrenia and who were at least 18 years of age. Patients with comorbid psychiatric diagnoses were not excluded from the sample. The inclusion criteria for the control group were any patients of at least 18 years of age admitted to the ED of the UPRH from January 2004 through December 2014 who did not have a diagnosis of mental illness. In the control group any patient with psychiatric diagnoses was excluded. Patients with less than 18 years old were excluded.

Definition of study variables

For our study, the response variable was defined as the presence or absence of a schizophrenia diagnosis, according to the hospital's identification or billing (CPT) codes. Moreover, the explanatory variable was defined as the presence or absence of any physical comorbidity, according to the CPT codes employed by the hospital (see section below).

Definitions of comorbid conditions under study

- *Cardiovascular diseases*: Those of the heart and vasculature, including hypertension, ischemic heart disease, peripheral vascular disease, cerebrovascular accidents, congestive heart failure, arrhythmias, and hyperlipidemias.
- *Endocrine diseases*: Those of the endocrine glands, excluding the ovaries and testes.
- *Hematologic diseases*: Those of any blood component.
- *Malignancy*: Any type of cancer.
- *Respiratory diseases*: Those of the upper and lower respiratory tracts.
- *Renal diseases*: Those of the upper urinary tract, only.

Demographic data

Demographic and other data, such as age, gender, date of admission, date of schizophrenia diagnosis, comorbid diseases, and smoking status, were obtained from the medical records of the participants.

Data collection methods

Medical records (electronic and paper) were screened for the schizophrenia billing code for the period of January 2004 through December 2014. An identical number of control cases were randomly selected and analyzed to determine whether they could be included.

Statistical analysis

A univariate statistical analysis with frequencies and percentages was done for every variable of the study; a median was calculated for the age variable. To establish statistical

associations between the case study and control group variables, a bivariate regression analysis and a test of significance were performed (OpenEpi Software, version 3.01) (12). Odd ratios (ORs) (with a 95% CI) were calculated, and Fisher's exact test for categorical variables was performed; both were done with the statistical program mentioned above. Stratification of the sample populations was performed by the potential confounding sociodemographic variables, including tobacco use and alcohol abuse and further examined with the Cochran–Mantel–Haenszel method. A Bonferroni adjustment was applied to control for multiple comparisons.

Ethical considerations

The study was reviewed by the San Juan Bautista School of Medicine Institutional Review Board and approved as protocol number EMSJBIRB-23-2016.

Results

Descriptive analysis of study population

A total of 223 patients were included in this study. The demographic characteristics of the study population are described in Table 1.

Table 1. Demographic distribution of patient cohorts

Characteristic	Schizophrenia *n (%)*	Non-schizophrenia *n (%)*
Gender		
Female	39 (34.5)	56 (51)
Male	74 (65.5)	54 (49)
Age		
<55 years	54 (47.8)	50 (45.5)
>55 years	59 (52.2)	60 (54.5)
Mean	55.4 years (SD ± 14.7)	56.1 years (SD ± 17.8)

Abbreviations: SD – standard deviation.

Frequency distribution of comorbid conditions

Frequency distributions were assessed for all the comorbid conditions in both the schizophrenia and the non-schizophrenia groups (Table 2). A higher frequency of cardiovascular pathologies was noted in the schizophrenia group (83.2%) compared to the control group (72.7%). Notably, within the CVD category, ischemic heart disease was more frequent in the schizophrenia (11.5%) compared to control (2.7%) group. Of note, a higher frequency of malignancies was encountered in the non-schizophrenia group (12.7%) than in the schizophrenia group (7.1%). Importantly, the average number of comorbid conditions present in the schizophrenia group was 2.16 compared to 2.26 in the control group (not shown).

Table 2. Frequency of comorbid conditions between patient groups

Disorder	Schizophrenia *n (%)*	Non-schizophrenia *n (%)*
Cardiovascular diseases	*94 (83.2)*	*80 (72.7)*
Hypertension	55 (48.7)	55 (50)
Ischemic heart disease	13 (11.5)	3 (2.7)
Congestive heart failure	7 (6.2)	3 (2.7)
Dysrhythmias	2 (1.8)	0 (0)
Peripheral vascular disease	4 (3.5)	6 (5.4)
Cerebrovascular accidents	9 (7.9)	2 (1.8)
Hyperlipidemias	4 (3.5)	11 (10)
Endocrine diseases	*55 (48.7)*	*51 (46.3)*
Diabetes mellitus	31 (27.4)	34 (31)
Thyroid disorders	17 (15)	10 (9.1)
Obesity	7 (6.2)	7 (6.4)
Hematologic diseases	*9 (7.9)*	*6 (5.4)*
Malignancy	8 (7.1)	14 (12.7)
Pulmonary diseases	*12 (10.6)*	*14 (12.7)*
Asthma	6 (5.3)	12 (10.9)
Chronic obstructive pulmonary disease	6 (5.3)	2 (1.8)
Renal Diseases	*9 (7.9)*	*7 (6.4)*
Renal failure	9 (7.9)	7 (6.4)

Prevalence of comorbid conditions

A prevalence analysis revealed CVD prevalences of 58.4% and 52.7% in the schizophrenia and non-schizophrenia groups, respectively, although a statistically significant difference was not observed (OR: 1.24 [95% CI: 0.73–2.1]; $P = .42$) (Table 3). Furthermore, in the patients with schizophrenia, we identified higher prevalences of thyroid disorders (15% vs. 9.1% [in the control group]; OR: 1.58 [95% CI: 0.85–2.96]; $P = .52$), anemia (6.2% vs. 5.5% [in the control group]; OR: 1.24 [95% CI: 0.52–2.97]; $P = .63$), COPD (5.3% vs. 1.8% [in the control group]; OR: 2.06 [95% CI: 0.62–6.78]; $P = .22$) and renal disease (8% vs. 6.4% [in the control group]; OR: 1.03 [95% CI: 0.47–2.25]; $P = .92$) than were identified in the control group, although the results were not statistically significant.

The prevalence of malignancies in the patients without schizophrenia was higher than was said prevalence in the patients with schizophrenia (11.8% vs. 6.2%, respectively; OR: 0.44 [95%

Table 3. Prevalence of comorbid conditions between patient groups

Disorder	Schizophrenia Prevalence (n = 113)	Non-schizophrenia Prevalence (n = 110)	OR* (95% CI)	*P* value
CVD[a]	58.4%	52.7%	1.24 (0.73–2.1)	.42
DM[b]	27.4%	30.9%	0.86 (0.56–1.34)	.52
Thyroid Disorders[b]	15.0%	9.1%	1.58 (0.85–2.96)	.16
Obesity[b]	6.2%	6.4%	0.81 (0.35–1.87)	.63
Anemia[b]	6.2%	5.5%	1.24 (0.52–2.97)	.63
Malignancy[a]	6.2%	11.8%	0.44 (0.22–0.88)	.01
Asthma[b]	5.3%	10.9%	0.42 (0.19–0.94)	.03
COPD[b]	5.3%	1.8%	2.06 (0.62–6.78)	.22
Renal Disease	8.0%	6.4%	1.03 (0.47–2.25)	.92

Adjusted for sociodemographic variables (former and current tobacco use and alcohol use) using the Cochran–Mantel–Haenszel test. [a]Patients with at least 1 of the comorbid conditions specified were grouped in a single category. [b]Within each disease category, these were the only comorbid conditions identified. Abbreviations: CVD – cardiovascular disease; DM – diabetes mellitus; COPD – chronic obstructive pulmonary disease.

CI: 0.22–0.88]; $P = .01$). Moreover, the prevalence of asthma was 10.9% in the control group compared to 5.3% in the schizophrenia group (OR: 0.42 [95% CI: 0.19–0.94]; $P = .03$). Additionally, the prevalence of DM was slightly higher in the control group than it was in the patients with schizophrenia (30.9% vs. 27.4%, respectively; OR: 0.86 [95% CI: 0.56–1.34]; $P = .42$).

Gender comparison of prevalence rates of comorbid conditions

To determine whether a higher rate of comorbid conditions exists in either male or female patients with and without schizophrenia, a prevalence study was carried out by further stratifying the gender subpopulations. Briefly, prevalence was calculated by measuring the presence of the specified disorder in the male (Figure 1A) and female (Figure 1B) patients with and without schizophrenia. A comparable sex distribution was observed, with a slightly higher percentage of male (57.4%) than female subjects (42.6%). In the male group, CVD was more prevalent in the patients with schizophrenia than it was I the patients without this disorder (55.4% vs. 44.4%, respectively; OR: 1.55 [95% CI: 0.76-3.17]; $P = .23$), whereas in the female group, the difference was not as discernible (66.7% and 62.5% [in the control group]; OR: 1.2 [95% CI: 0.51-2.88]; $P = .69$).

Thyroid disease had a prevalence of 19.9% in the male subjects with schizophrenia compared to only 1.9% in those without (OR: 9.14 [95% CI: 1.49–204.4]; $P = .01$); the prevalences of this condition were comparable in the female patients, being 17.9% in the schizophrenia group and 16.1% in the non-schizophrenia group (OR: 1.14 [95% CI: 0.37–3.44]; $P = .81$). Statistical significance was not found in the remaining comorbid conditions.

Age comparison of prevalence rates of comorbid conditions

We performed a prevalence analysis by stratifying the patients with and without schizophrenia by age. Specifically, we analyzed the rate of prevalence of comorbid somatic conditions in patients with and without schizophrenia who were less than 55 years old (Figure 2A) and in their counterparts who were 55 years old and older (Figure 2B). The prevalence of CVD in the patients under 55 years of age with schizophrenia was 61.8% compared to 51.7% in those in the non-schizophrenia group (OR: 1.5 [95% CI: 0.54–4.19]; $P = .44$). In the patients who were 55 years old and older, the CVD prevalences were 91.8% and 81.1% in the patients with and without schizophrenia, respectively (OR: 2.59 [95% CI: 0.77–10.18]; $P = .13$).

Consistent with previous findings (Figure 1), the prevalences of thyroid disorders were higher in the patients with schizophrenia in both age groups (23.5% vs. 13.8% [in the patients without schizophrenia and aged <55 years]; OR: 1.9 [95% CI: 0.51–

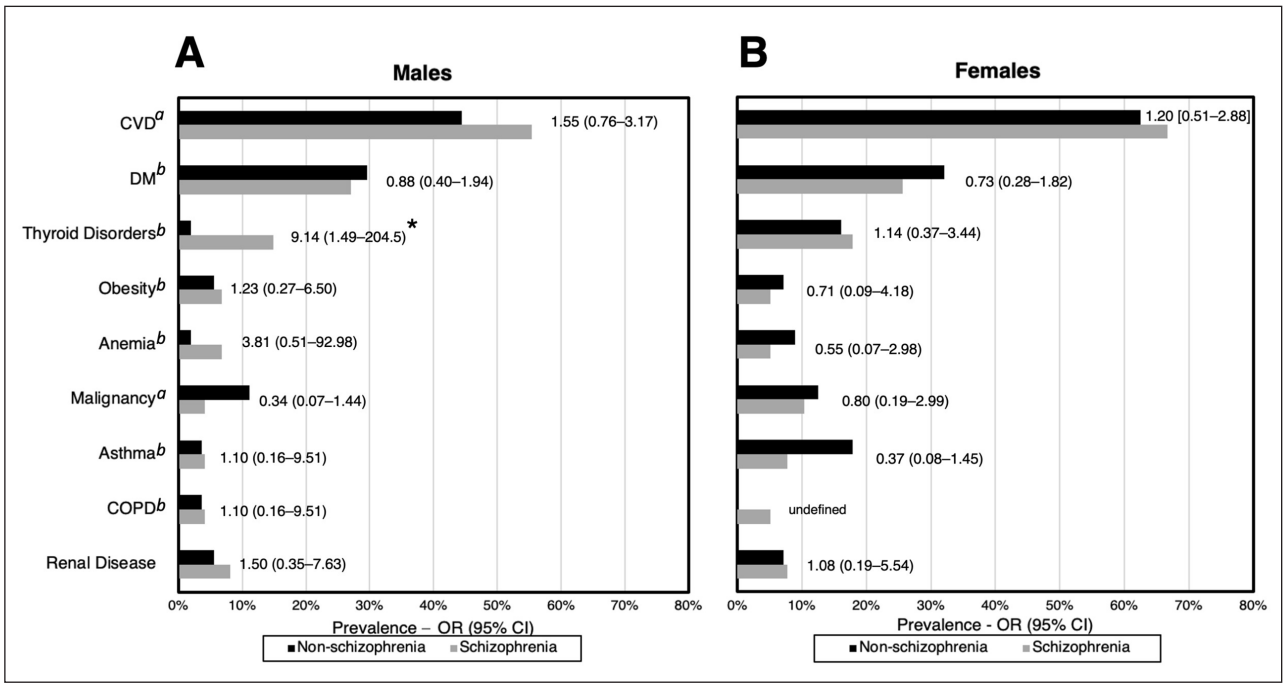

Figure 1. Comparison (by gender) of prevalence rates of comorbid conditions in patients with and without schizophrenia. Prevalence was calculated by measuring the presence of the specified disorder in male (A) and female (B) patients with and without schizophrenia. A total of 128 male subjects were studied, of whom 74 suffered from schizophrenia and 54 did not (A). Within the female group (B), 39 subjects suffered from schizophrenia and 56 did not, for a total of 95 patients. The odds ratio was adjusted for sociodemographic variables (former and current tobacco use and alcohol use) using the Cochran–Mantel–Haenszel test. aPatients with at least 1 of the comorbid conditions specified were grouped in a single category. bWithin each disease category, these were the only comorbid conditions identified. *P ≤ .05. Abbreviations: CVD – cardiovascular disease; DM – diabetes mellitus; COPD – chronic obstructive pulmonary disease.

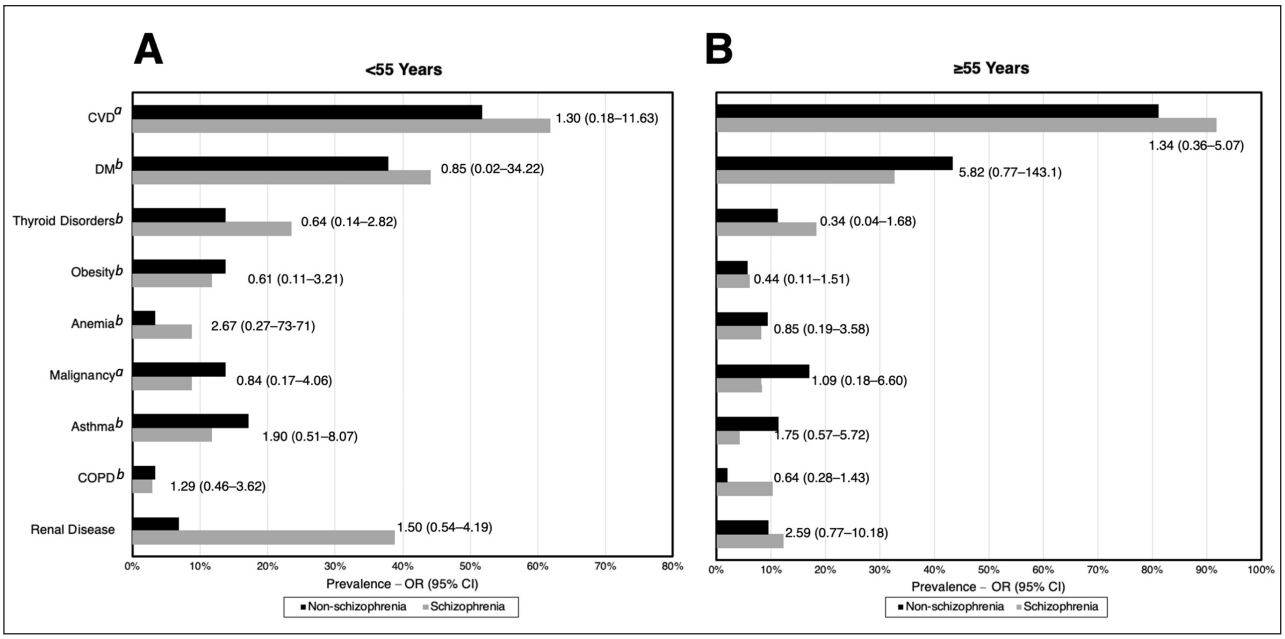

Figure 2. Comparison (by age) of prevalence rates of comorbid conditions in patients with and without schizophrenia. Prevalence was calculated by measuring the presence of the specified disorder in patients aged <55 years (A) and in those aged 55 years and over (B) with and without schizophrenia. A total of 63 patients aged <55 years were studied, of whom 34 had schizophrenia and 29 did not (A). Within the group of patients who were at least 55 years of (B), 49 had schizophrenia and 53 did not, for a total of 102 patients. The odds ratio was adjusted for sociodemographic variables (former and current tobacco use and alcohol use) using the Cochran–Mantel–Haenszel test. aPatients with at least 1 of the comorbid conditions specified were grouped in a single category. bWithin each disease category, these were the only comorbid conditions identified. Abbreviations: CVD – cardiovascular disease; DM – diabetes mellitus; COPD – chronic obstructive pulmonary disease.

8.07]; $P = .35$, and 18.4% vs. 11.3% [in the control group, aged ≥55 years]; OR: 1.75 [95% CI: 0.57–5.72]; $P = .33$).

The prevalence of renal disease in the patients under 55 years old with schizophrenia was markedly high (38.8%) compared to that of those without schizophrenia (6.9%; OR: 1.3 [95% CI: 0.18–11.63]; $P = .81$). Further, the prevalence of COPD was higher in the patients with schizophrenia who were 55 years old and older (10.2%) compared to that of the control group of the same age (1.9%; OR: 5.82 [95% CI: 0.77–143.1]; $P = .1$). The remaining comorbid conditions were similarly distributed across age groups. Overall, the findings of age effects across subgroups did not reach statistical significance.

Discussion

Patients with schizophrenia have increased morbidity and mortality rates compared to the general population.(1) Cardiovascular disease is the most common natural cause of death in patients with schizophrenia.(7) In PR, schizophrenia is the most frequently treated severe mental illness (SMI); however, no studies have been conducted to establish the prevalence of CVD in adult Puerto Rican patients with schizophrenia. To our knowledge, this is the first study to establish such a prevalence rate in this vulnerable population.

First, the frequency distribution of comorbid conditions was analyzed in our population sample. A higher frequency of CVD was noted in the patients with schizophrenia compared to those in the control group. Although hypertension was by far the most frequent pathology encountered in both groups and in comparable distribution, ischemic heart disease was approximately 4 times more frequent in the patients with schizophrenia. These findings are consistent with those of other reports (13,14) and are possibly related to the obesity and cardiometabolic derangements caused by the use of second-generation antipsychotics.(15,16) Although the mechanisms for these detrimental effects remain unknown, a randomized clinical trial is underway to determine whether this population should be concomitantly managed with metformin.(17) Moreover, a higher frequency of malignancies was encountered in the patients without schizophrenia than in those with this disorder. While some reports have suggested that schizophrenia has a protective effect against cancer,(18-20) this remains a highly controversial assertion.

Furthermore, as disclosed above, a prevalence analysis was carried out in our study population. There was a trend towards a higher prevalence of CVD in the patients with schizophrenia. At this juncture, we recognize that this is in alignment with previous investigations (5,11) and said trend should be further explored. When stratification by age and gender was performed, we did not observe a significant difference between subgroups, although a trend towards a higher prevalence of CVD in female patients 55 years old and

older with schizophrenia was noted. These patients might benefit the most from the intense mitigation of cardiometabolic risk factors and strategies aimed to prevent such factors from arising.

Additionally, thyroid disease was more prevalent in the patients with schizophrenia than it was in their non-schizophrenic counterparts (Table 3); this is thought to be due to associated genetic aberrations that predispose individuals to abnormalities in the hypothalamic–pituitary–thyroid axis, which abnormalities are secondary to neuroleptic intake. (21,22) Interestingly, an age comparison of prevalence rates revealed a statistically significant higher prevalence of thyroid dysfunction in men than women while age had no apparent effect. This finding merits further investigation.

As previously mentioned, and in agreement with our initial results, a statistically significant higher prevalence of cancer was encountered in the patients without schizophrenia. This apparent protective factor was not explained in terms of gender or age, and further investigation is warranted. Moreover, the prevalence of asthma in the patients without schizophrenia was almost twice that of those with schizophrenia, and when a comparison was made by gender, women were found to be more affected than men were, while age did not appear to have an effect. This finding is inconsistent with past reports (23,24) and should be further investigated.

Our study had limitations. The effect estimates herein described are based on retrospectively collected data from a single institution, which data were derived from the patients with and without schizophrenia. Therefore, the data are subject to potential selection bias and confounders. Although we attempted to control for some of these factors in subsequent stratification analyses, we recognize this inherent limitation and the consequently low generalizability of our findings. Additionally, we were unable to characterize the prevalences of the various comorbid conditions in our study group, likely due to the limited sample size. We hope our study will support future clinical investigations that explore this relevant issue.

Moreover, potential reasons behind our having obtained statistically non-significant results are that the prevalence rates for CVD were unexpectedly higher in people living in PR, in general, and that our analysis was in fact underpowered. Furthermore, we should note that the patients in the control group were not medically stable, as they were admitted to the hospital due to a variety of medical conditions. Importantly, a lack of statistical significance should not suggest that pragmatic or clinically important effects do not exist.

In conclusion, these findings should motivate healthcare workers to work on a systematic approach to prioritize the aggressive management, early diagnosis, and prevention of comorbid risk factors in patients with SMI, especially in female patients older than 55 years with schizophrenia. To reduce the risk of comorbid risk factors in patients with schizophrenia, coordinated interventions in different health care settings are necessary. There is a need to develop and implement lifestyle-intervention programs to decrease comorbid risk factors in patients with schizophrenia. More importantly, our work could generate an opportunity to design and implement key public health initiatives to mitigate this important issue and decrease public expenditure.

Conclusion

In conclusion, SMI, particularly schizophrenia, is strongly associated with reduced life expectancy and thus poses a vast financial burden; CVD is the leading cause of premature death in this group. Extensive literature portrays this population as inherently vulnerable to metabolic dysfunction and CVD, while underscoring the fact that the routine use of antipsychotic medication further exacerbates the predisposition of the members of this population to these diseases.

Understanding the risks of comorbid general medical conditions is of utmost importance, both for clinicians and for patients with schizophrenia. Closer attention to the prevention, early diagnosis, and management of CVD may decrease the associated morbidity and mortality and improve prognoses among this patient population.

Resumen

Objetivo: Los pacientes con esquizofrenia tienen una mayor tasa de mortalidad en comparación con la población general siendo la enfermedad cardiovascular (ECV) la principal causa de muerte. Nuestra meta es identificar la prevalencia de ECV y otras condiciones comórbidas en pacientes con esquizofrenia que viven en Puerto Rico. Métodos: Se realizó un estudio descriptivo retrospectivo de casos y controles. Los sujetos de este estudio fueron ingresados al hospital Dr. Federico Trilla entre 2004 y 2014 por afecciones psiquiátricas y no psiquiátricas. La estratificación de las poblaciones de la muestra se realizó mediante variables que incluyen el uso de tabaco y abuso de alcohol, y se analizó con el método de Cochran–Mantel–Haenszel. Resultados: Se observó una mayor frecuencia de ECVs en pacientes con esquizofrenia en comparación con el grupo control. La hipertensión fue la patología más frecuentemente encontrada en ambos grupos. Sin embargo, la cardiopatía isquémica fue aproximadamente cuatro veces más frecuente en pacientes con esquizofrenia. La prevalencia de ECV representó el 58.4% y el 52.7% en los grupos de esquizofrenia y no esquizofrenia, respectivamente, aunque sin una diferencia significativa. La prevalencia de neoplasias malignas en pacientes sin esquizofrenia fue mayor 11.8 % frente a 6.2 % en el grupo de esquizofrenia. Además, la prevalencia de asma fue del 10.9% en el grupo control frente al 5.3% en el grupo de esquizofrenia. Conclusión: Los profesionales de la salud deben trabajar de forma sistemática para priorizar el manejo, el diagnóstico temprano y la prevención de los factores de riesgo comórbidos en pacientes con esquizofrenia.

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