

CARDIOVASCULAR RISK FACTORS FOR DIFFERENT TYPES OF PSYCHIATRIC PATHOLOGIES. A CORRELATIVE STUDY

GABRIELA RADU^{1#}, AURORA DIANA BORDEJEVIC^{1#}, VALENTINA BUDA^{2*}, MIRELA CLEOPATRA TOMESCU¹, IOAN DRAGAN³, LIANA DEHELEAN⁴, IONUT LUCIAN COCOS⁵, ADELINA CHEVERESAN⁶, MINODORA ANDOR¹

¹Department of Internal Medicine I, Medical Semiology II, "Victor Babeș" University of Medicine and Pharmacy, Timișoara, Romania

²Department of Pharmacology and Clinical Pharmacy, "Victor Babeș" University of Medicine and Pharmacy, Timișoara, Romania

³Department of Medical Informatics and Biostatistics, "Victor Babeș" University of Medicine and Pharmacy, Timișoara, Romania

⁴Department of Neurosciences - Psychiatry, "Victor Babeș" University of Medicine and Pharmacy, Timișoara, Romania

⁵Department of Psychiatry, "Teodor Andrei" Hospital City, Lugoj, Romania

⁶Department of Pharmacology, "Victor Babeș" University of Medicine and Pharmacy, Timișoara, Romania

*corresponding author: buda.valentina.oana@gmail.com

#Authors with equal contribution.

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Abstract

Cardiovascular diseases (CVD) and psychiatric severe illnesses (PSI) are the leading causes of morbidity and mortality worldwide and the link between CVD and PSI has been studied for decades. The aim of this study was to evaluate the impact of classical cardiovascular risk factors (age, sex, smoking status, alcohol, arterial hypertension, lipid profile) and Framingham Score for the 10-year risk of death from cardiovascular diseases, in different types of severe mental illnesses. On the basis of the premise that patients with psychiatric illness have a life expectancy of 10 - 17.5 years less than the general population, predominantly associated with cardiovascular disease, we conducted a retrospective study of 165 patients admitted in the psychiatric clinic for a period of 1 year. Cardiovascular risk factors as well as other risk factors for cardiovascular disease (presence of associated medication, renal function, alcohol use) were calculated for all 165 patients. The mean systolic blood pressure was 136.7 mmHg (patient group) compared with 130 mmHg (control group); total cholesterol was 244 mg/dL (patient group) compared with 187.2 mg/dL (control group); and high-density lipoprotein (HDL) cholesterol was 36.7 mg/dL (patient group) compared with 46.4 mg/dL (control group). In addition, the Framingham score was 12.7 in the group of PSI patients compared with 5.47 in the control group. According to our results, the patients with severe mental illness were clearly all at an increased risk of cardiovascular-related death compared with the control group, odds ratio (OR) = 4.030. The highest OR was found in patients with Alzheimer's disease (OR = 62.171), but also in patients with severe depression (OR = 4.371), and patients with schizophrenia (OR = 3.288). On the basis of these results, clinicians should screen all psychiatric patients for increased body mass index, elevated blood pressure, and cholesterol, and begin medical treatment and non-medical intervention to decrease this cardiovascular risk as soon as possible.

Rezumat

Bolile cardiovasculare (CVD) și bolile grave psihiatrice (PSI) sunt principalele cauze ale morbidității și mortalității la nivel mondial, iar legătura dintre CVD și PSI a fost studiată de zeci de ani. Scopul acestui studiu a fost evaluarea impactului factorilor de risc cardiovascular clasici (vârstă, alcool, hipertensiune arterială, profil lipidic) și scorul Framingham pentru riscul de deces pe 10 ani din boli cardiovasculare, în diferite tipuri de boli psihiatrice severe. Pe baza premisei că pacienții cu patologie psihiatrică au o speranță de viață cu 10 - 17,5 ani mai mică comparativ cu populația generală, asociată predominant bolilor cardiovasculare, am efectuat un studiu retrospectiv care a inclus 165 de pacienți cu patologie specifică internată în clinica de psihiatrie pentru o perioadă de 1 an. Factorii de risc cardiovascular, precum și alți factori de risc pentru bolile cardiovasculare (medicamentele asociate, funcția renală, consumul de alcool) au fost calculate pentru toți cei 165 de pacienți. Presiunea arterială sistolică medie a fost de 136,7 mmHg (grup pacienți) comparativ cu 130 mmHg (grup control); colesterolul total a fost de 244 mg/dL (grup pacienți) comparativ cu 187,2 mg/dL (grup control) și a HDL colesterolului 36,7 mg/dL (grup pacienți) comparativ cu 46,4mg/dL (grup control). În plus, scorul Framingham a fost de 12,7 la grupul de pacienți cu PSI, comparativ cu 5,47 la lotul control. Conform rezultatelor noastre, pacienții cu boli psihiatrice severe prezentau în mod clar un risc crescut de mortalitate de cauză cardiovasculară, comparativ cu grupul control, OR = 4,030. Cel mai mare OR a prezentat grupul de pacienți cu boală Alzheimer (OR = 62,171), dar și cei cu schizofrenie (OR = 3,288). Pe baza acestor rezultate, clinicienii ar trebui să analizeze toți pacienții cu patologie psihiatrică pentru indicii de masă corporală, tensiune arterială, colesterol, crescute, și să înceapă tratamentul farmacologic și non-farmacologic pentru a reduce acest risc cardiovascular cât mai devreme posibil.

Keywords: cardiovascular diseases, psychiatric severe illnesses, cardiovascular risk factors

Introduction

Cardiovascular diseases (CVD) and psychiatric severe illnesses (PSI) are the leading causes of morbidity and mortality worldwide [27, 44]. The link between the CVD and PSI has been studied for decades and different types of connections have been suggested between the two high-burden diseases. A higher prevalence of CVD among PSI patients has been demonstrated in several studies [1, 4, 15].

Pathologies such as schizophrenia, schizoaffective disorder, bipolar disorder, depressive disorders with psychotic symptoms or treatment-resistant depressive disorders without psychotic symptoms (augmentation therapy), delusional disorder, acute and transient psychotic disorder require symptomatic treatment based on neuroleptics (antipsychotics) (Table I) [2, 41]. Antipsychotics, formerly known as major tranquilizers, are classified according to their chemical structure, but more importantly, to their pharmacodynamic profile, which determines their antipsychotic potency, side effects, and spectrum of use (Table I). First generation

antipsychotics, also known as neuroleptics, or conventional or typical antipsychotics, block dopamine D2 receptors with frequent extrapyramidal side effects. A higher affinity for the D2 dopamine correlates with a stronger clinical response (Table I). Second-generation antipsychotics, also called atypical antipsychotics, have a dual serotonin 2A and dopamine 2 antagonism with less extrapyramidal, endocrine, or cognitive side effects. Some antipsychotics like sulpiride and amisulpride have a partial D2 receptor agonism modulating dopamine levels. At lower doses, they increase dopamine release enhancing cognition, while at higher doses; they block dopamine D2 receptors acting as antipsychotic agents. Aripiprazole, sometimes referred as a third-generation antipsychotic, is a fair example of a partial dopamine 2 agonist, acting as a D2 agonist or antagonist depending on synaptic dopamine levels and stabilizing the dopaminergic system. Antipsychotics that share a partial agonism on serotonin 1A receptors have antidepressant actions and are also used in mood disorders (Table I) [41].

Table I

Classification of antipsychotics according to their pharmacodynamic profile

Conventional/Typical antipsychotics (Dopamine 2 antagonists)		Atypical antipsychotics (Serotonin 2A Dopamine 2 antagonists) - SDA			Dopamine partial agonists - DPA
D2 receptor antagonism	D2 receptor antagonism with partial D2 agonism (dose - related)	With serotonin 1A receptor partial agonism - SPA	Without serotonin receptor 1A partial agonism	With serotonin 1A partial agonism and partial D2 agonism - SDA+SPA+DPA	D2 receptor antagonism with partial D2 agonism (dose - related)
Chlorpromazine	Sulpiride	Clozapine	Asenapine	Aripiprazole*	Amisulpride
Flupentixol		Quetiapine	Olanzapine	Cariprazine**	
Haloperidol		Ziprasidone	Paliperidone		
Loxapine			Risperidone		
Zuclopenthixol			Sertindole		

* more affinity for D2 receptor than D3, ** more affinity for D3 receptor than D2

The chronic, neurodegenerative pathology, Alzheimer’s disease (AD) is the major cause of dementia nowadays. Although its cause is poorly understood, it seems that hypercholesterolemia, diabetes, hypertension, and smoking aggravate its course, being risk factors for vascular dementia. There are currently two drug classes that are used in the treatment of cognitive deficits related to AD: cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and N-methyl-D-aspartate (NMDA) glutamate receptor antagonists such as memantine. They show efficiency in the early phases of AD or when combined. Atypical antipsychotics can be prescribed for associated psychological and behavioural symptoms (psychosis, mood and sleep disturbances, wandering or aggression) [24].

The aim of this study is to evaluate the impact of classical cardiovascular risk factors (age, sex, smoking status, alcohol, arterial hypertension, lipid profile) and Framingham Score [3] for the 10-year risk of death from cardiovascular diseases in different types of severe mental illnesses.

Materials and Methods

On the basis of the premise that patients with psychiatric illnesses have a life expectancy of 10 - 17.5 years less than the general population [28], predominantly associated with CVD [19], we conducted a retrospective study on 165 patients admitted to our psychiatric clinic for a period of 1 year. Cardiovascular risk factors (age, sex, smoking status, lipid profile, blood pressure values) as well as other risk factors for CVD (presence of associated medication, renal function and alcohol use) were calculated for all 165 patients.

Most similar studies selected healthy subjects for the control group, making causal interpretations of the differences between the groups difficult. In our study, the control group was deliberately selected from hospitalized patients (with various diseases), to reveal whether the psychiatric patients do have similar cardiovascular parameters to these control subjects. The selection of the control group was randomly performed from an initial pool of 305 patients, hospitalized during the same period in the Internal Disease Clinic of City

Hospital of Timișoara, Romania, to match age groups and gender proportions with the studied group. The 171 patients of the control group were examined regarding the risk of CVD, after the same parameters had been determined.

The criteria for inclusion were as follows: the long-term hospitalization of patients with PSI, without a history of coronary heart disease or intermittent claudication or other atherosclerotic disease, undergoing psychiatric treatment. Medical files were searched for the following information: demographics, including sex, age, living area, clinical information of the participants, including diagnosis, duration of hospitalization, history of other medical illnesses, including hypertension, diabetes, medication intake, social habits including smoking status, alcohol intake and diet.

Blood pressure was measured using a mercury sphygmomanometer on the right arm of each participant in a sitting position after a 30 minutes rest period. Blood pressure was expressed as the mean value of three measurements over a period of 30 minutes. Blood pressure was considered high when systolic blood pressure was ≥ 140 mmHg, or diastolic blood pressure was ≥ 90 mmHg. Patients were considered hypertensive, according to their medical file, if they were treated with antihypertensive medication. Blood samples were collected from the antecubital vein between 6:00 a.m. and 7:00 a.m. after at least 12 hours of fasting and were immediately centrifuged. Glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol were assessed using routine laboratory methods at the hospital. High total cholesterol was defined as ≥ 200 mg/dL, low HDL-C was defined as $\text{HDL-C} \leq 40$ mg/dL.

The diagnosis of diabetes was established based on at least 2 elevated glucose values of ≥ 126 mg/dL of the basal blood glucose obtained on different days and/or self-reported treatment of diabetes with anti-diabetic medication in the previous two weeks.

Smoking status was classified in terms of current smokers or non-smokers (including ex-smokers).

Habitual alcohol consumption was defined as drinking twice *per* month over the past 12 months, regardless of the quantity of alcohol consumed.

The Framingham/ATP III criteria were used to estimate the 10-year risk of death by coronary heart disease (CHD). The risk predictor algorithm was proposed for non-diabetic patients, age 30 - 79 years, with no prior history of coronary heart disease or intermittent claudication. Calculation of the Framingham 10-year risk of hard CHD included predictors factors such as age, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, and smoking status. Patients were assigned in one of two categories according to their 10-year hard CHD risk: under 10% (low risk), over 10% (high risk).

According to the diagnosis of the patients during hospitalization, we divided the 165 psychiatric patients into 5 groups: patients with schizophrenia or other schizoaffective disorder (A), patients with bipolar disorder (B), patients with severe depression (C), patients with other mental illnesses like retardation, or psychosis due to organic disease (D), and Alzheimer’s disease (E). We assessed the cardiovascular risk factors for each group and the Framingham Score was calculated. The study was carried out according to the Helsinki Declaration Guidelines [48]. The protocol of the study and the Informed Consent of the patients were approved by the Scientific Research Ethic Committee of “Victor Babeș” University of Medicine and Pharmacy Timișoara, Romania

The statistical analysis was performed using IBM SPSS Statistic (version 20). A χ^2 (chi-square) test was used for categorical variables. For the risk analysis, the odds ratio (OR) values and their confidence intervals were calculated using EpiInfo.

Results and Discussion

In our study, 165 consecutive admitted patients with PSI were included (82 males and 83 females), with a mean age of 54.34 years old. This group was compared with the control group (171 patients: 87 males and 84 females, mean age 54.30 years old), admitted in the same period of time in the Internal Medicine Clinic. The two groups had no significant differences regarding age and sex distribution (Table II).

Table II
Demographic data of the studied patients

	Patients						Control					
	Total		M (male)		F (female)		Total		M (male)		F (female)	
	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
n	165		82		83		171		87		84	
Smoking	62	103	40	42	22	61	23	148	17	70	6	78
Alcohol	53	112	42	40	11	72	8	163	8	79	0	84
	med	dv.st.	med	dv.st.	med	dv.st.	med	dv.st.	med	dv.st.	med	dv.st.
Age (years)	54.3	12.1	53.5	11.2	55.2	13.0	54.3	12.2	52.4	12.4	56.3	11.6
SBP (mmHg)	136.7	13.4	135.7	13.0	137.8	13.8	130.0	6.6	129.9	6.7	130.1	6.5
Cholesterol (mg/dL)	244.0	54.3	239.9	53.1	248.0	55.6	187.2	33.5	184.6	35.7	189.9	31.0
HDL-c (mg/dL)	36.7	1.9	36.9	1.9	36.5	1.9	46.4	7.2	44.5	6.0	48.4	7.9
Framingham score	12.70	9.89	16.55	10.33	8.90	7.81	5.47	5.87	8.13	6.59	2.72	3.23

The mean values of systolic blood pressure were significantly higher in the patient's group (136.7 mmHg) comparing with the control group (130.1 mmHg), also the total cholesterol was higher in the PSI patient's group (244.0 mg/dL) than in the control group (187.2 mg/dL) and HDL-cholesterol is lower in the patient's group (36.7 mg/dL) comparing with the control group (46.4 mg/dL). As a result of these, the

Framingham score is higher in the PSI patients (12.70) comparing with the control group (5.47) (Table II). Regarding the control of the habits which can influence the cardiovascular outcome, in the group of patients with psychiatric disorders, the use of alcohol was increased compared with the control group (32.1% vs. 4.7%, $p < 0.001$), and also the smoking status (37.6% vs. 13.5%, $p < 0.001$) (Table III).

Table III

Composition and codification of metronidazole gel formulations

	Patients						Control					
	Total		M		F		Total		M		F	
	%	N	%	N	%	N	%	N	%	N	%	N
Smoking	37.6	165	48.8	82	26.5	83	13.5	171	19.5	87	7.1	84
Alcohol	32.1		51.2		13.3		4.7		9.2		0.0	

To identify better the cardiovascular risk factors according to the psychiatric disease, we divided the group of patients with PSI into five different groups and we assessed the cardiovascular risk factors and the Framingham score of each group. According to our results, all the subgroups were homogenous regarding the sex distribution, with no significant differences when compared with the control group. From the data presented in Tables IV and V, we found that the group of patients with schizophrenia

or schizoaffective disorders had values significantly increased for total cholesterol (293.3 vs. 187.2, $p < 0.001$) and Framingham score (10.15 vs. 5.47, $p < 0.001$) and significantly decreased for HDL-cholesterol (36.7 vs. 46.4, $p < 0.001$), even though their mean age was significantly lower than in the control group (48.8 vs. 54.3, $p = 0.004$). The values of systolic blood pressure were not significantly different from the control group.

Table IV

Comparison between different psychiatric diseases

	Patients												Control	
	Total		Schizophrenia		Bipolar		Depression		Alzheimer		Other PSI		Total	
n	165		48		9		51		17		40		171	
M/F	82	83	22	26	5	4	31	20	8	9	17	23	87	84
	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Smoking	62	103	24	24	3	6	20	31	1	16	14	26	23	148
Alcohol	53	112	12	36	1	8	23	28	2	15	15	25	8	163
	med	dv.st.	med	dv.st.	med	dv.st.	med	dv.st.	med	dv.st.	med	dv.st.	med	dv.st.
Age	54.3	12.1	48.8	10.7	57.1	8.6	55.0	10.8	71.0	7.0	52.5	11.2	54.3	12.2
SBP (mmHg)	136.7	13.4	132.0	9.7	140.6	15.5	138.9	14.8	148.5	13.3	133.8	11.4	130.0	6.6
Cholesterol (mg/dL)	244.0	54.3	239.3	57.9	256.7	26.6	254.8	59.1	261.4	41.3	225.6	48.6	187.2	33.5
HDL-c (mg/dL)	36.7	1.9	36.7	1.9	36.6	1.3	36.8	1.9	36.9	2.3	36.6	1.9	46.4	7.2
Framingham score	12.70	9.89	10.15	8.42	12.57	11.58	13.00	9.09	23.45	8.36	10.83	10.09	5.47	5.87

PSI = psychiatric severe illnesses

In the group with bipolar disease, there were also significant changes regarding the total cholesterol (256.7 mg/dL), HDL-cholesterol (36.6 mg/dL), and Framingham Score (12.57), while the age and values of systolic blood pressure were similar compared with the control group.

In the group with severe depression, even when age was comparable with the control group, all the determined parameters considered to have impact on the early CVD were deteriorated (cholesterol 254.8 mg/dL, HDL-c 36.8 mg/dL, Framingham score 13.0) to a statistically significant level.

The group with Alzheimer's disease had very significant differences in all the studied parameters regarding

the cardiovascular risk, but statistical interpretation is difficult because of the significantly higher age than the control group (71.0 vs. 54.3, $p < 0.01$).

In the group with PSI from various aetiologies, the age was comparable with the control group, and the cardiovascular risk parameters, except systolic blood pressure, were modified in the sense of increased cardiovascular risk when compared to the control group.

It is interesting to remark that HDL had almost the same average change in all patients, regardless the type of psychiatric pathology.

Table V

p values - comparison between different groups of psychiatric patients and control group (n = 171)

Test		Total	Schizophrenia	Bipolar	Depression	Alzheimer	Other PSI
	n	165	48	9	51	17	40
Chi-sq	M/F	0.829	0.537	0.785	0.215	0.764	0.341
	Smoking	< 0.001	0.007	0.099	< 0.001	0.374	0.001
	Alcohol	< 0.001	< 0.001	0.389	< 0.001	0.216	< 0.001
Mann-Whitney	Age	0.861	0.004	0.404	0.893	< 0.001	0.367
	SBP	0.004	0.891	0.102	0.007	< 0.001	0.556
	Cholesterol	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
	HDL-c	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
	Framingham score	< 0.001	< 0.001	0.014	< 0.001	< 0.001	0.001

PSI = psychiatric severe illnesses

According to the data from Table VI, we can observe that the group with schizophrenia had a higher percent of smokers (50%) and alcohol use (25%) than the control group (smoking 13.5% and alcohol use 4.7%).

The patients with severe depression (smoking 39% and alcohol use 45.1%) and patients with other PSI (smoking 35% and alcohol use 37.5%) also had higher percentages than the control group.

Table VI

Smoking and alcohol consumption in different groups of psychiatric patients

	Patients												Control	
	Total		Schizophr.		Bipolar		Depression		Alzheim.		Other psy.		Total	
	%	N	%	N	%	N	%	N	%	N	%	N	%	N
M/F	49.7	165	45.8	48	55.6	9	60.8	51	47.1	17	42.5	40	50.9	171
Smoking	37.6		50.0		33.3		39.2		5.9		35.0		13.5	
Alcohol	32.1		25.0		11.1		45.1		11.8		37.5		4.7	

Risk analysis

Noting the increased values of cardiovascular risk factors in all subgroups of psychiatric patients, we calculated the OR for SBP, total cholesterol, HDL, and the Framingham Score.

It is interesting to note that the values of OR for HDL are very high, showing a very strong deviation of values in the patient group from the values in the control group. Moreover, it is very high for all psychiatric pathologies.

For the Framingham score, a value higher than 10% shows that the risk of cardiovascular death from a cardiovascular disease in the next 10 years is more than 10%. All the psychiatric patients had a higher risk of cardiovascular death than the control group (OR = 4.030). An extremely high OR was found in the group of patients with Alzheimer’s disease (OR = 62.171), which may have been due to the group being older than the control group, but this was also seen in the patients with severe depression (OR = 4.371) and patients with schizophrenia (OR = 3.288). Psychiatric diseases have a complex etiopathogenesis, involving numerous cellular mechanisms, as well as modifications of the associated behaviours, which increases the risk of CVD [18]. It is also known that second-generation antipsychotic medication, through antagonizing various postsynaptic receptors (alpha1, muscarinic, histaminic H1), have side effects associated with dyslipidaemia, hyperglycaemia and obesity, which result in increased cardiovascular risks [20, 26]. It should also be noted that mental stress can cause

endothelial dysfunction, which increases the risk of cardiovascular damage in healthy people [39].

It is known from the literature that patients with schizophrenia have a higher risk of cardiovascular disease [14, 35] and of acute myocardial infarction compared to the general population [29, 36, 45].

Our study is consistent with the data from the literature, finding an OR = 3.288 compared to the control group, which was deliberately chosen from a population hospitalized for different CVD pathologies in an Internal Medicine Clinic.

Patients with bipolar disorder have the lowest risk of developing CVD from all the studied subgroups (OR = 1.934) and have lower levels of addictive behaviours associated with cardiovascular risk [49] than other patient groups. However, in longitudinal studies, the risk of this category of patients for CVD was considered statistically significant [33].

Severe depression is known to be linked to cardiovascular disease in both directions [46], severe cardiovascular disease causes depression and severe depression causes cardiovascular disease [33, 46]. These findings compelled the American Heart Association (AHA) to recommend that depression be considered a poor prognostic factor after acute coronary syndrome [21, 32]. This recommendation officially highlights the first psychiatric variable as a risk factor for a poor outcome after myocardial infarction. The risk of death in these patients within the next 10 years from cardiovascular disease is very high (OR = 4.371). The risk factors for this category of patients are statistically

significant in the sense of high risk, with smoking [30] and alcohol consumption being very high [15].

The subgroup of patients diagnosed with Alzheimer's disease, which was found to present a huge risk of death from CVD (OR = 62.171), must be interpreted from several perspectives. The group of patients with Alzheimer's disease had a higher average age, which increases the risk of death in the next 10 years. There are also established studies that have elucidated similar mechanisms regarding the etiopathogenesis of Alzheimer's disease and atherosclerotic disease [37], such as a common genetic and behavioural background [42]. Hypertension is identified as an independent factor for Alzheimer's disease [5-7, 10]. There are theories about the etiopathogenesis of Alzheimer's disease related to vascular wall thickening and blood vessel occlusion, a pathology that is generated by atherosclerosis [43].

Other severe mental illnesses are recognized in the literature as having a high cardiovascular risk [11, 23]. A large-scale Swedish study (N = 1,107,524) showed a clear association between severe mental illness, including personality disorders, alcohol abuse related disorders and the use of other substances with an increased cardiovascular risk [25].

The contributors to the increased cardiovascular risk in psychiatric patients are, besides changes in lipid profile, high blood pressure, fatty diet, smoking and harmful alcohol use [22, 38], as well as biological and genetic factors [13, 31]. The biological mechanisms involved in the association between severe psychiatric diseases and cardiovascular diseases are autonomic nervous system dysfunction (which causes decreased heart rate variability, hypertension, increased QT variability and increased QT dispersion), hypothalamo-pituitary-adrenal axis dysfunction, inflammation (mostly endothelial inflammation), oxidative stress, and increased platelet reactivity [8, 9, 12, 16, 17, 34, 40, 47].

The limitations of this study include the fact that routine clinical data may be less extensive in terms of cardiovascular risk variables than cohorts designed for research. The patients who were already diagnosed with diabetes, in both cohorts (admitted in the psychiatric department and in the Internal Medicine Clinic), were excluded because diabetes is not included in the calculation of the Framingham Score. Sufficient data were not available to examine the consequence of antipsychotic drugs, which are known to increase the cardiovascular risk by themselves.

Conclusions

The efforts, to improve the clinical condition and decrease the mortality of patients with PSI, need to address the cardiovascular risk factors, which are a major contributor to the excess burden in all psychiatric patients. According to our results, the patients with severe mental illnesses were clearly all at an increased

risk of cardiovascular-related death compared with the control group. On the basis of these results, clinicians should screen all psychiatric patients for increased body mass index, elevated blood pressure, and cholesterol, and begin medical treatment and non-medical intervention to decrease these cardiovascular risks as soon as possible.

Conflict of interest

The authors declare no conflict of interest.

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