THE PREVALENCE OF CARDIOMETABOLIC RISK FACTORS AND THE TEN-YEAR RISK OF FATAL CARDIOVASCULAR EVENTS IN PATIENTS WITH SCHIZOPHRENIA AND RELATED PSYCHOTIC DISORDERS

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SUMMARY

Background: People suffering from schizophrenia have a significantly shorter lifespan compared to the general population. The majority of deaths are caused by physical diseases, including cardiovascular events. The aim of this cross-sectional study was to predict the risk of premature cardiovascular mortality and assess the prevalence of cardiometabolic risk factors in a sample of Czech patients with schizophrenia and related psychoses.

Subjects and methods: We reviewed data from 129 subjects treated in an outpatient clinic that specialised in psychoses. The main collected variables included basic physical parameters (height, weight, waist circumference, blood pressure), smoking habits, laboratory data (glucose level, serum lipid level) and an electrocardiograph (ECG). We calculated the ten-year risk of fatal cardiovascular events using the Systematic Coronary Risk Evaluation (SCORE) chart.

Results: The most prevalent risk factors were being overweight (70% of patients had a BMI over 25), dyslipidaemia (70% of patients) and smoking (43% of patients). According to the SCORE diagram, there was a high risk of fatal cardiovascular events over a ten-year period in 10% of the study group. The percentage was even higher (24%) when the latest European guidelines for cardiovascular disease prevention were used to calculate the risk.

Conclusions: Our outcomes indicate even higher cardiometabolic morbidity rates in patients with psychoses than those referenced in the literature.

Key words: *schizophrenia – cardiovascular - risk factor - mortality*

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INTRODUCTION

Patients suffering from schizophrenia have at least a 20-year shorter lifespan compared to the general population (Newcomer 2007), and this mortality gap has widened in recent decades (Weinmann et al. 2009). Approximately 60% of this excess mortality is caused by somatic diseases (Leucht et al. 2007). Patients with schizophrenia suffer from a spectrum of somatic disorders similar to the general population, but they die at a younger age. Mortality due to cardiovascular diseases is doubled in patients with schizophrenia. The reason lies partly in the increased prevalence of general cardiovascular risk factors in this population, such as obesity, hyperglycaemia, hypertension, dyslipidaemia and smoking (De Hert et al. 2008). However, the mechanisms leading to increased cardiometabolic risk in schizophrenia patients have not yet been fully elucidated (Saari et al. 2005).

One of the cardinal factors modifying the cardiometabolic risk in schizophrenia patients is their lifestyle. An unhealthy diet, lack of exercise and alcohol consumption lead to obesity, which subsequently increases the risk of other disorders, such as hypertension, dyslipidaemia, diabetes, osteoarthritis and disorders of the coronary arteries, respiratory system and gallbladder. Smoking is considered to be an individual cardiovascular risk factor. The prevalence of smoking in schizophrenia patients is increased two- to three-fold compared to the general population (Saari et al. 2005).

Long-term treatment with antipsychotic drugs in patients with schizophrenia is essential for the good management of symptoms and improvement of their prognosis. Moreover, the overall mortality of patients on maintenance antipsychotic treatment has been observed to be lower than the mortality of their untreated companions (Tiihonen et al. 2009). However, one of the established side effects of antipsychotics, affecting between 15% and 72% of patients, is weight gain. Increased weight may be associated with hyperlipidaemia and insulin resistance. Moreover, antipsychotics (predominantly the atypical ones) may have a weight-unrelated diabetogenic potential, presenting as a potentially fatal condition called diabetic ketoacidosis in rare cases (Melkersson & Dahl 2004, De Hert et al. 2011). In addition to weight gain and glucose dysregu-

lation-related mechanisms, there appears to be a direct increasing effect of antipsychotics on cardiovascular risk. There is evidence that higher doses of anti-psychotics predict a greater risk of mortality from coronary heart disease and cerebrovascular accident (De Hert et al. 2011).

In some patients, there are considerable metabolic disturbances present already at the onset of psychosis, before the initiation of antipsychotic therapy. Results of a large prospective study conducted in the Netherlands showed that 21% of first-episode patients had increased cholesterol levels. First-episode patients also had relatively increased amounts of intra-abdominal fat compared to subcutaneous fat stores (De Hert et al. 2009). It is well known that abdominal obesity is a significant cardiovascular risk factor. These findings support the hypothesis that metabolic disturbances are a part of schizophrenia itself.

On the other hand, data from a large meta-analysis including 25 692 unique patients with schizophrenia from 27 countries or regions suggest that one of the major determinants for higher risk of metabolic syndrome is longer illness duration. Metabolic syndrome is a group of abnormal metabolic findings that are predictive for cardiovascular disease and its prevalence was 13% in first-episode patients compared to 35.3% in patients who were neither drug naïve nor in their first episode (Mitchell et al. 2011). Based on such findings, the long-term management and monitoring of cardiometabolic health of schizophrenia patients should be considered essential.

Nevertheless, cardiometabolic risk factors and related diseases are still insufficiently detected and treated in patients with severe mental illnesses, including schizophrenia (De Hert et al. 2008, Bernando et al. 2009; Kozumplik et al. 2010). This is partly because these patients fail to seek medical care themselves due to poor motivation, lack of insight and decreased ability for self-care. Conversely, many somatic doctors tend to avoid severely mentally ill patients and minimise the care provided to them, mainly because communication with these individuals is difficult, and the doctors are uncomfortable with the contact due to an inadequate understanding of mental illness itself.
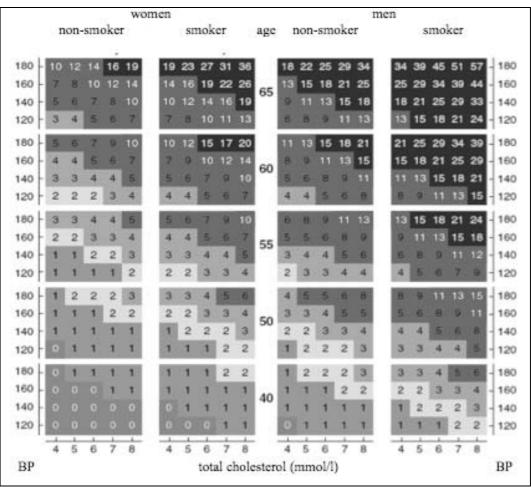
The aim of the present study was to assess the prevalence of individual cardiometabolic risk factors and to determine the cardiovascular risk in a sample of Czech patients with schizophrenia and related psychoses. We tested the hypothesis that patients with schizophrenia possess a significantly higher risk of cardiovascular diseases compared to the general population. Moreover, we anticipated an even higher prevalence of cardiometabolic risk factors in our sample compared to patients with schizophrenia in other parts of Europe due to the increased prevalence of those risk factors in the Czech population in general (Cifkova et al. 2005).

SUBJECTS AND METHODS

We reviewed the data of 129 outpatients treated in an outpatient clinic that specialised in psychoses in the Psychiatric clinic of the University Hospital in Hradec Kralove. Inpatients in acute psychotic state were not included in order to prevent the stress-related endocrine changes from interfering with the metabolic results. All of the patients were diagnosed with psychosis, and 67% had a diagnosis of schizophrenia according to the ICD-10 criteria. In total, 60% of the subjects were male, with an average age of 36 years (±11.9). The females were significantly older (47±14.4 years). In the study group, 75% of individuals were receiving incapacity benefits (n=97), 8% were retired (n=10), and 17% were employed or were searching for a job. The average length of psychiatric care was 14 years (±11). The majority of the patients (96%, n=125) were treated with antipsychotics; 95 patients were receiving monotherapy, and 30 patients were treated with a combination of two or three antipsychotic agents. Atypical antipsychotics were used in 89% of the patients, and 25 patients were also taking antidepressants or mood stabilisers.

For the purpose of a cross-sectional analysis, we reviewed patient files from the year 2009. The analysed parameters included the following: family history of cardiovascular disease, smoking status, blood pressure, BMI (body mass index), waist circumference, chole-sterol levels, LDL (low density lipoprotein), HDL (high density lipoprotein), glucose levels, triglyceride levels and electrocardiograph (ECG) results. The prevalence of individual cardiometabolic risk factors was deter-mined according to NCEP (National Cholesterol Education Program) guidelines. Dyslipidaemia was defined as an elevation of cholesterol or triglyceride levels above the normal range, as defined by the central laboratory of the University Hospital in Hradec Kralove. We used the Systematic Coronary Risk Evaluation (SCORE) chart to detect patients at high risk for fatal cardiovascular events over a ten-year period (Conroy et al. 2003). The SCORE risk assessment system is derived from a large dataset of prospective European studies. To predict a fatal atherosclerotic endpoint, it integrates the following risk factors: gender, age, smoking, systolic blood pressure and total cholesterol. The numbers in the diagram represent the percentage of risk over ten years, with the threshold of being at high risk defined as ≥5% (Figure 1). The chart has been adjusted for the Czech population based on mortality data collected by UZIS (Institute of Health Information and Statistics of the Czech Republic) and the values of the risk factors in the Czech MONICA (Monitoring trends and determinants in Cardiovascular disease) and Czech post-MONICA (Cifkova et al. 2010) studies.

We used a one-way ANOVA and the Mann-Whitney U test for the statistical analysis of the collected variables. Significant results were defined as having a p value greater than 0.05, and highly significant results

SCORE: Systematic Coronary Risk Evaluation (stratifies the ten-year risk of fatal cardiovascular events; numbers represent percentage of risk; high risk ≥ 5), BP: blood pressure

Figure 1. The SCORE system for the Czech Republic (adapted from Cifkova et al. 2005)

had a p value greater than 0.001. The demographic data, pharmacotherapy and presence of cardiometabolic risk factors in the study group are presented as percentages and means with standard deviations. Means and standard deviations were also used for the physical and laboratory variables. The gender differences between individual risk factors were analysed by the Pearson χ^2 test.

Approval by an ethical committee and written informed consent were not required because all of the analysed variables were collected as part of an annual screening of patients according to good medical practice, and the study itself did not influence patient examinations, pharmacotherapy or social care by any means. None of the addressed patients refused to participate in the annual screening procedures.

RESULTS

In the study group, dyslipidaemia was the most frequent of the cardiometabolic risk factors and was present in 70% of the patients. Detailed information is shown in Table 1. Gender differences were apparent

only in smoking status, where significantly more male patients were smokers. The physical and laboratory data are presented in Table 2. Fifty per cent of the patients had a BMI value greater than 27, which is considered to be a threshold for increased risk of cardiovascular disease. The male patients had significantly higher weights, waist circumferences and diastolic blood pressures compared to female patients. Regarding the laboratory parameters, the male patients had significantly lower HDL blood levels. According to NCEP criteria, 69.8% of the patients had a BMI value above the normal range (greater than 25), 46.5% of the patients had high cholesterol levels, and 64.7% of the patients had a waist circumference above the set normal range. Detailed data are shown in Table 3.

According to the SCORE chart, there were 13 patients (10%) with a high (≥ 5%) ten-year risk of fatal cardiovascular events. When the European guidelines on cardiovascular disease prevention (Cifkova et al. 2005) were applied to our study group, the percentage of patients with a high risk of fatal cardiovascular events over a ten-year period reached 24%. No differences were found between genders.

Table 1. Prevalence of the basic risk factors of cardiovascular disease

Gender	Smoking (%)*	HN (%)	DM (%)	CV (%)	Dyslipidaemia (%)
Males	47 (60%)	12 (15%)	9 (12%)	2 (2%)	57 (73%)
Females	9 (18%)	8 (16%)	7 (14%)	0 (0%)	33 (65%)
Total	56 (43%)	20 (16%)	16 (12%)	2 (2%)	90 (70%)

HN: hypertension, DM: diabetes mellitus, CV: personal history of cardiovascular disease;
*(Pearson $\chi2$ = 22.79048 df=1 p<0.001)

Table 2. Mean values of physical and laboratory parameters

Parameter	Mean (SD)			
	males	females	total	
BMI	27.7 (4.8)	28.2 (4.8)	27.9 (4.7)	NS
Weight	88.4 (15.6)	77.9 (12.6)	84.2 (15.3)	+ ANOVA
WC	98.8 (11.7)	94.6 (12.8)	97.2 (12.3)	* K-S
Systolic BP	127.9 (12.3)	124.5 (14.5)	126.6 (13.3)	* M-W U
Diastolic BP	72.5 (13.5)	72.6 (11.0)	72.6 (12.5)	NS
QTc	390.1 (27.7)	394.6 (27.3)	391.9 (27.5)	NS
HDL	1.16 (0.27)	1.43 (0.46)	1.27 (0.38)	*M-W U
LDL	3.19 (0.90)	3.20 (0.96)	3.19 (0.92)	NS
Cholesterol	5.06 (1.05)	5.18 (1.13)	5.10 (1.08)	NS
Glycaemia	5.63 (1.26)	5.69 (1.58)	5.65 (1.39)	NS
TG	2.01 (2.06)	1.53 (0.88)	1.82 (1.71)	NS

BMI: body mass index, WC: waist circumference, BP: blood pressure, QTc: corrected interval on the ECG curve, HDL: high
density lipoprotein, LDL: low density lipoprotein, TG: triglycerides; * p<0.05; + p<0.001; M-W U: Mann-Whitney U Test;
K-S: Kolmogorov-Smirnov Two-Sample Test; NS: nonspecific

Table 3. Prevalence of cardiometabolic risk factors (patients with pathological values according to the National Cholesterol Education Program)

CM risk factor	No. of patients	Percentage
Fasting glycaemia > 7 mmol/l	10/129	7.75%
Triglycerides > 1.69 mmol/l	48/129	37.20%
Cholesterol > 5.17 mmol/l	60/129	46.50%
HDL < 1.03 mmol/l	39/129	30.20%
LDL $\geq$ 3.36 mmol/l	48/129	37.20%
BP $\geq$ 140/90	30/129	23.30%
WC - males > 102 cm	29/78	37.20%
WC - females > 88 cm	33/51	64.70%
BMI $\geq$ 25	90/129	69.80%

CM: cardiometabolic, HDL: high density lipoprotein, LDL: low density lipoprotein, BP: blood pressure, WC: waist
circumference, BMI: body mass index

DISCUSSION

We found a high prevalence of cardiometabolic risk factors in our study group. We compared the results of the female patients with those from a study conducted in 433 hospitalised Czech females treated with atypical antipsychotics (Svestka et al. 2007). Our female patients had a higher prevalence of diabetes (12% vs. 3.9%), hypertension (16% vs. 8.8%), increased weight (67% vs. 40%) and smoking (18% vs. 12%). The reason for such differences might lie in the higher average age of our female patients (47±14 years vs. 40.6±7.6 years) and the longer duration of maintenance psychiatric care (14.5 years vs. 7.6 years).

In a Spanish cross-sectional study of 733 patients with schizophrenia, the most prevalent cardiometabolic risk factor was smoking (71% of patients), followed by hypercholesterolaemia (66% of patients) (Bernando et al. 2009). The percentages in our group were 43% and 46.5%, respectively. Conversely, we observed a higher prevalence of obesity (68% of patients compared to 24% in the Spanish study). The prevalences of diabetes, hypertension and hypertriglyceridaemia were similar in both groups. Six point five 6.5% of the patients had a high ten-year risk of fatal cardiovascular event estimated by SCORE. Such a low percentage of patients at high risk of fatal cardiovascular event within ten years was probably due to a generally low risk of

cardiovascular disorders in that particular Spanish geographical area. In accordance with this hypothesis, another large Spanish cross-sectional study with multicentre design found that based on SCORE there were 8% of patients with schizophrenia and related disorders with a high risk of ten-year cardiovascular endpoint (Bobes et al. 2007). However, due to a different evaluation of SCORE (patients with SCORE ≥3% were considered a high risk individuals) and a very selective group of study participants (outpatients treated with only one antipsychotic drug) we could not compare the results with our data.

In a cohort of 28,775 Canadian patients with schizophrenia, the authors found a similar prevalence of diabetes (10.3% vs. 12% in our group) and hypertension (22.7% vs. 16%, respectively), but a much lower prevalence of dyslipidaemia (23% vs. 70%, respectively) compared to our group (Bresee et al. 2010). We suspect that the explanation for such a low prevalence of dyslipidaemia is the retrospective design of the Canadian study, where all of the data regarding diseases were based on diagnostic codes in patients' files. In such a situation, patients with undiagnosed dyslipidaemia would not be included in the analysis.

The basic characteristics of the study group in the CATIE (Clinical Antipsychotic Trial of Intervention Effectiveness) study also included some of the cardiometabolic risk factors (Daumit et al. 2008). The prevalence of diabetes (12%) was exactly the same in the American population of patients with schizophrenia (n=1125) and in our study group, but they had a higher prevalence of smoking (58% vs. 43% in our group) and hypertension (34% vs. 16%, respectively) and a higher average BMI. Cardiovascular risk in the CATIE study was calculated according to the Framingham risk score, which made the comparison with our data difficult.

The differences in data regarding cardiometabolic risk factors in patients with schizophrenia among different countries and geographical areas were reported in the recent extensive meta-analysis of 126 analyses in 77 publications from 27 countries and regions (Mitchell et al. 2011). The authors have found significantly higher rates of obesity (by waist size), hypertension, and abnormal HDL cholesterol in studies from the United States compared with other countries.

The SCORE system has been developed for assessing cardiovascular risk in asymptomatic subjects. Individuals with current cardiovascular disease, diabetes mellitus type 2 or type 1 with microalbuminuria and significantly increased values of specific risk factors (total cholesterol ≥ 8 mmol/l, blood pressure ≥180/110) should automatically be considered at high risk for fatal cardiovascular events over a ten-year period (Conroy et al. 2003). Based on such criteria, almost a quarter of our study group (24%) was already at high risk for fatal cardiovascular endpoints. Moreover, both the European and Czech associations of medical societies for cardiovascular disease prevention have identified cases

in which the absolute cardiovascular risk is even higher than that calculated based on the SCORE chart and the criteria above. The following groups are considered to be at higher risk: obese, inactive or socially deprived individuals; individuals with signs of preclinical atherosclerosis (diagnosed by ultrasound or ankle-brachial index); patients with a family history of cardiovascular disease; patients with low HDL and high triglyceride levels or with impaired glucose tolerance; individuals with elevated hsCRP (high-sensitivity C-reactive protein), fibrinogen, homocysteine, apolipoprotein B or lipoprotein(a) (Cifkova et al. 2005, Graham et al. 2007). For instance, our study group included 15% of obese individuals assessed as having low cardiovascular risk. Hence, the real cardiovascular risk might have been higher than calculated and might have included more patients.

Analysis of the association between cardiometabolic risk and individual antipsychotics has not been conducted due to the small number of patients in each drug group.

Except from a small study sample the presented study has several limitations. The study has a cross-sectional design and includes only outpatients from one selected psychiatric centre and geographical area. There is no control group from a general population and also the patient population was not controlled for dietary habits, physical activity and alcohol or drug abuse. Nevertheless, to the authors' best knowledge, the present study is the first to comprehensively assess the prevalence of cardiometabolic risk factors in a Czech population of patients with schizophrenia. Moreover, it allows further prospective follow-up and management of cardiometabolic disturbances in the study population.

Monitoring and treatment of cardiometabolic disorders in the severely mentally ill is still insufficient. In a group of 2463 patients with schizophrenia from 12 European countries, 10.9% of the patients were treated for hypertension, 7.1% were treated for dyslipidaemia, and 3.5% received treatment for diabetes type 2. The numbers are alarming, considering that ordinary screenings, including physical examinations and basic laboratory checks, revealed hypertension in 39%, dyslipidaemia in 70% and hyperglycaemia in 26% of examined individuals from the study group. In the CATIE study, the authors identified 88% of patients with dyslipidaemia, 62% of patients with hypertension and 38% of patients with diabetes who were not properly diagnosed and had received no treatment for their physical disorders (De Hert et al. 2009).

Considering this situation and the increasing cardiovascular morbidity of patients with psychosis, psychiatric associations have released a number of guidelines regarding cardiometabolic risk factor monitoring in patients on antipsychotic medications. In the case of established cardiometabolic abnormalities, the European Psychiatric Association recommends educating patients about the harmful effects of smoking and the benefits of

a healthy lifestyle. It also recommends considering a medication switch and a consultation with a general practitioner regarding antihypertensives, statins or antidiabetic medications (2001). Based on the finding that a fast initial weight gain of 7% or more after starting an antipsychotic medication predicts further significant increases in weight, the American Psychiatric Association recommends switching patients with such initial weight gain to a different antipsychotic drug, but only if their mental status allows for such a change (2004). Similar guidelines have also been published in the Czech Republic (Masopust & Maly 2010). Apart from a precise schedule for monitoring cardiovascular risk factors, the above authors also suggest an examination by a specialist in all patients with a high ten-year risk of fatal cardiovascular events or with highly pathological values of individual cardiometabolic risk factors revealed by recommended screenings.

On the basis of known impact of unhealthy lifestyle of patients with schizophrenia on their cardiometabolic health, the interest in benefits of physical activity in this population is growing. Different research groups have issued guidelines including recommendations regarding the amount and type of physical activity appropriate for schizophrenia patients. However, according to the recent review of correlates of physical activity in patients with schizophrenia, the correlate most consistently associated with lower participation in physical activity was the presence of cardio-metabolic comorbidity. Conversely, the knowledge on cardiovascular risk factors was an important positive correlate (Vancampfort et al. 2011). Such finings suggest that proper monitoring, treatment and education about cardiometabolic risk factors could improve some of the aspects of a schizophrenia patients' lifestyle.

CONCLUSION

In agreement with the set hypothesis, we found a high prevalence of cardiometabolic risk factors in our group of patients with schizophrenia and related psychotic disorders. A high ten-year risk of fatal cardiovascular events was detected in 24% of the patients. This number is higher than that referenced in the literature and may be related to the high cardiometabolic morbidity of the Czech population in general.

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