

Prevalence of Metabolic Syndrome Among Patients with Schizophrenia in Singapore

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Abstract

Introduction: Schizophrenia has been associated with an increased risk of cardio-metabolic morbidity and mortality. Metabolic syndrome (MetS), a reliable predictor of cardiovascular-related morbidity and mortality, has also been shown to be more prevalent in patients with schizophrenia. In this study, we investigated the prevalence of MetS in a sample of patients with schizophrenia in Singapore, and the potential risk factors associated with it. **Materials & Methods:** One hundred patients with schizophrenia and 300 community controls were recruited. All subjects provided a fasted sample of venous blood to measure high-density lipoprotein cholesterol (HDL-C), triglycerides and glucose levels. Weight, height and waist circumference were measured. Presence of MetS was assessed according to the American Heart Association and the National Heart, Lung and Blood Institute (AHA/NHLBI) guidelines. **Results:** The prevalence of MetS in patients with schizophrenia was 46.0%. The adjusted odds ratio (OR) for MetS among patients was 2.79 (CI, 1.50 to 5.20, $P = 0.001$) when compared with controls. Increasing body mass index (BMI) was identified to be significantly associated with the prevalence of MetS. **Conclusion:** This study found a high prevalence of MetS in Singapore patients with schizophrenia, and that BMI might be a risk factor in the development of MetS. This information is clinically relevant as BMI is routinely measured in psychiatric practice today, and could be used to monitor for development of MetS in schizophrenia.

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Introduction

Schizophrenia has been linked to metabolic disturbances such as obesity, dyslipidaemia and hyperglycaemia.¹ It has also been associated with a more than 3-fold increase in mortality associated with cardiovascular causes.² This increase in cardio-metabolic morbidity and mortality might be due to several factors such as inherent genetic vulnerability or environmental exposures such as smoking, sedentary lifestyle, antipsychotic medication and gaps in healthcare access.^{3,4}

Metabolic syndrome (MetS) is defined by a cluster of clinical features, including increased visceral adiposity, hyperglycaemia, hypertension and dyslipidaemia.⁵ Currently, there are at least 6 different classification criteria for MetS developed by various expert panels.⁶ Some of the

commonly applied criteria in a clinical setting are those by the International Diabetes Foundation (IDF) and the American Heart Association and the National Heart, Lung and Blood Institute (AHA/NHLBI). They have also been applied to a large number of studies. Although the causes of MetS are not well understood, studies have consistently shown it to be a strong predictor of cardiovascular morbidity, mortality, and diabetes. Therefore, MetS has become of clinical interest as almost all the criteria symptoms are potentially modifiable risk factors.

MetS is highly prevalent in patients with schizophrenia with reported prevalence that ranges from 10.1% to 69.3%.⁷⁻¹⁴

These estimates appear higher than that in the community and could be an intermediate step in the development of

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subsequent cardiovascular disease and eventual mortality. Therefore, it is important to screen for MetS and identify associated modifiable risk factors for MetS in patients with schizophrenia. In Singapore, the prevalence of MetS in the community had been reported to range from 17.7% to 26.2% depending on the criteria adopted. MetS in Singapore had been associated with a 3-fold increase in cardiovascular mortality.^{15,16}

Body mass index (BMI), a measure of human body fat, is a commonly used measure in clinical practice to monitor for development of obesity. However, waist circumference was included in the criterion for MetS instead because it more closely approximates central obesity. In this study, we hypothesised that patients with schizophrenia have an increased prevalence of MetS compared to the general population. In addition, we hypothesised that increasing BMI is a significant factor associated with MetS.

Materials and Methods

Subjects

This study was conducted at the Institute of Mental Health (IMH), the only psychiatric hospital in Singapore. Eligible patients were recruited from outpatient clinics and inpatient units of IMH. All eligible patients were interviewed by a clinician, and clinical notes reviewed to determine the diagnosis of schizophrenia prior to study inclusion. Patients aged 21 and above were enrolled into the study if they fulfilled diagnostic criteria for schizophrenia established using the structured clinical interview for DSM-IV-TR Axis I Disorders (SCID-I) with no history of organic brain disorders or mental retardation. Controls enrolled were defined as community-dwelling individuals with no history of psychiatric disorders. Controls were recruited via advertisements or referrals. Ethics approval for this study was given by the National Healthcare Group Domain Specific Review Board. Only subjects capable of providing written informed consent were recruited for this study.

Assessments

A standardised data collection form was used in the gathering of information. Demographic information, medical and smoking histories were obtained from the subjects. Those who smoked were further categorised into those who smoked 10 or less cigarettes a day and those who smoked more than 10 cigarettes a day to evaluate for dose response relationship to MetS. Height and weight of subjects were measured, and BMI was calculated. BMI was further categorised into underweight (BMI <18.5 kg/m²), low risk (BMI 18.5 to 22.9 kg/m²), moderate risk (23.0 to 27.4 kg/m²) and high risk (BMI ≥27.5 kg/m²) according to the World Health Organisation (WHO) public health action

points for Asians.¹⁷ Waist circumference was measured in the standing position. Subjects were seated when blood pressure was measured. A sample of blood was collected after an overnight fast. High-density lipoprotein cholesterol (HDL-C), triglycerides and glucose levels were measured with the analyzer LX-20PRO (Beckman Coulter, Germany) from the serum content of subjects using standard analytical protocols. Duration of illness for patients with schizophrenia was defined as the duration from onset of first psychotic symptom to the date of recruitment. Current antipsychotic prescriptions were recorded and doses were converted into total daily chlorpromazine equivalents.^{18,19}

Metabolic Syndrome Classification

We adopted the AHA/NHLBI criteria for metabolic syndrome in our study as it has been found to be most sensitive in predicting the prevalence of cardiovascular disorder in a Singaporean cohort.^{5,16} This criterion included elevated triglycerides (≥150 mg/dL or on drug treatment for elevated triglycerides), reduced HDL-C (≤40 mg/dL in males and ≤50 mg/dL in females or on drug treatment for reduced HDL-C), elevated blood pressure (≥130 mmHg systolic blood pressure or 85 mmHg diastolic blood pressure or on drug treatment for hypertension), and elevated fasting glucose (≥100 mg/dL or on drug treatment for elevated glucose). We used Asian waist circumference cut-offs of ≥90 cm for males and ≥80 cm for females for central obesity as it has been validated in a Singaporean cohort.²⁰ Individuals are considered to suffer from metabolic syndrome if they fulfilled at least 3 of the above mentioned criteria.

Statistical Analysis

Statistical analyses were performed using Predictive Analytics Software Statistics (PASW) version 18. Descriptive statistics were tabulated for patients and controls, and for those with and without MetS. Statistical significance was performed with the chi-squared test for categorical variables, and student's t-test for continuous variables. Statistically significant variables were entered into the logistic regression model that comprised the entire sample to estimate the adjusted odds ratio (OR) of MetS in patients with schizophrenia. The similar approach was used to identify factors associated with MetS in the patient sample. Criterion variables for classification of MetS were not selected into the model to avoid over-adjustment of the effects of the schizophrenia disease. The adjusted OR, 95% confidence intervals (CI) and *P* values were computed from both models. With 100 cases and 300 controls, and assuming that 18.3% of controls suffer from MetS (with Mets), and alpha = 0.05, we have at least 80% power to detect an OR of 2.2 or more.

Results

One hundred patients with schizophrenia and 300 healthy controls were recruited into the study. Of these 100 patients recruited, only 2 were inpatients at the time of recruitment, and the remaining 98 were recruited from outpatient clinics. Table 1 shows the demographics and metabolic characteristics of the study sample. The patient group had a higher proportion of males, smokers, and metabolic disturbances such as obesity, hypertension, hypertriglyceridaemia and fasting hyperglycaemia.

One hundred and one (25.3%) subjects were identified to have MetS according to the AHA/NHLBI criterion. Other than the variables involved in the criteria for MetS, those with MetS were significantly older with a mean age of 38.1 years (SD 7.5) compared with those without MetS with a mean age of 34.3 years (SD 8.1) ($P < 0.001$). Those with MetS had a significantly higher BMI compared with those without MetS, with the mean BMI at 28.5 kg/m² (SD 4.7) and 23.2 kg/m² (SD 4.0) respectively ($P < 0.001$). There were also 10.6% more males ($P = 0.018$) and 8.8% more smokers ($P = 0.030$) in the group with MetS.

Table 1. Characteristics of Study Subjects

	Controls (n = 300)	Patients (n = 100)	P value
Age in years, mean (SD)	34.9 (8.2)	36.6 (7.5)	0.066
Gender, n (%)			0.023
Male	159 (53.0)	66 (66.0)	
Female	141 (47.0)	34 (34.0)	
Ethnicity, n (%)			0.945
Chinese	244 (81.3)	84 (84.0)	
Malay	24 (8.0)	7 (7.0)	
Indian	28 (9.0)	8 (8.0)	
Others	4 (1.3)	1 (1.0)	
Smoking status, n (%)			<0.001
Non-smokers	276 (92.0)	69 (69.0)	
≤10 cigarettes a day	21 (7.0)	12 (12.0)	
>10 cigarettes a day	3 (1.0)	19 (19.0)	
Body Mass Index in kg/m², n (%)*			<0.001
Underweight, <18.5	16 (5.3)	9 (9.0)	
Low risk, 18.5 to 22.9	126 (42.0)	20 (20.0)	
Moderate risk, 23 to 27.4	100 (33.3)	34 (34.0)	
High risk, ≥27.5	58 (19.3)	37 (37.0)	
Metabolic syndrome, n (%)†	55 (18.3)	46 (46.0)	<0.001
Elevated waist circumference, n (%)‡	146 (48.7)	64 (64.0)	0.008
Elevated triglycerides, n (%)§	49 (16.3)	44 (44.0)	<0.001
Reduced HDL-C, n (%) 	118 (39.3)	44 (44.0)	0.410
Elevated blood pressure, n (%)¶	98 (32.7)	48 (48.0)	0.006
Elevated fasting glucose, n (%)#	56 (18.7)	32 (32.0)	0.005
Duration of illness in years, mean (SD)		12.16 (7.18)	
Daily CPZ** equivalent in mg, mean (SD)		295.8 (267.3)	
Type of antipsychotic prescribed, n (%)			
Typical		39 (39.0%)	
Atypical		37 (37.0%)	
Typical and atypical		24 (24.0%)	

*Body mass index is categorised according to WHO public health action points for Asians

†Metabolic syndrome as defined by AHA/NHLBI criterion

‡Defined by waist circumference ≥90cm for males and ≥80cm for females following Asian cutoffs

§Triglycerides ≥150 mg/dL or on drug treatment for elevated triglycerides

|| ≤40 mg/dL in males and ≤50 mg/dL in females or on drug treatment for reduced HDL-C

¶ ≥130 mmHg systolic blood pressure or 85 mmHg diastolic blood pressure or on drug treatment for hypertension

≥100 mg/dL or on drug treatment for elevated glucose

** Chlorpromazine

A significantly higher prevalence of MetS was found in patients (46.0%) compared to controls (18.3%). Table 2 displays the characteristics between patients with and without MetS. More smokers and higher BMI were noted in patients with MetS. There were no differences in duration of illness, or current antipsychotic doses in chlorpromazine equivalents. There were also no differences in typical or atypical antipsychotic usage between those with and without MetS.

Patients with schizophrenia had an unadjusted OR of 3.80 (CI 2.33 to 6.19, $P < 0.001$) for MetS. After inclusion of significant variables in the model, such as age, gender, smoking and BMI, the adjusted OR for MetS in schizophrenia was 2.79 (CI 1.50 to 5.20, $P = 0.001$) (Table 3).

Table 2. Characteristics of Patients with and without Metabolic Syndrome

	MetS present (n = 46)	MetS absent (n = 54)	P value
Age in years, mean (SD)	37.6 (7.0)	35.5 (8.0)	0.193
Gender, n (%)			0.786
Male	31 (67.4)	35 (64.8)	
Female	15 (32.6)	19 (35.2)	
Ethnicity, n (%)			0.530
Chinese	37 (80.4)	47 (87.0)	
Malay	4 (8.7)	3 (5.6)	
Indian	5 (10.9)	3 (5.6)	
Others	0 (0.0)	1 (1.9)	
Smoking status, n (%)			0.073
Non-smokers	27 (58.7)	42 (77.8)	
≤10 cigarettes a day	6 (13.0)	6 (11.1)	
>10 cigarettes a day	13 (28.3)	6 (11.1)	
Hypertensive (%)	36 (78)	12 (26)	<0.001
Body Mass Index in kg/m², n (%)*			<0.001
Underweight, <18.5	1 (2.2)	8 (14.8)	
Low risk, 18.5 to 22.9	2 (4.3)	18 (33.3)	
Moderate risk, 23 to 27.4	15 (32.6)	19 (35.2)	
High risk, ≥27.5	28 (60.9)	9 (16.7)	
Duration of illness in years, mean (SD)	13.5 (7.15)	11.0 (7.06)	0.060
Daily CPZ† equivalent in mg, mean (SD)	314.9 (235.9)	279.6 (292.6)	0.070
Type of antipsychotic prescribed, n (%)			0.098
Typical	23 (50.0)	16 (29.6)	
Atypical	15 (32.6)	22 (40.7)	
Typical and atypical	8 (17.4)	16 (29.6)	

*Body mass index is categorised according to WHO public health action points for Asians

†Chlorpromazine

Table 3. Logistic Regression of Adjusted Risk of Schizophrenia on Metabolic Syndrome

Variables	Odds ratio	95% CI	P value
Schizophrenia*	2.79	1.50 to 5.20	0.001
Age	1.06	1.02 to 1.10	0.004
Male†	2.04	1.14 to 3.65	0.017
Smokers‡			
≤10 cigarettes a day	0.65	0.22 to 1.88	0.427
>10 cigarettes a day	1.36	0.43 to 4.31	0.065
Body Mass Index§			
Underweight, <18.5	0.47	0.05 to 4.26	0.500
Moderate risk, 23 to 27.4	5.00	2.17 to 11.50	<0.001
High risk, ≥27.5	19.50	8.29 to 45.95	<0.001

*Controls being the reference group

†Female being the reference group

‡Non-smokers being the reference group

§Low risk BMI, 18.5 to 22.9 being the reference group

BMI and MetS in Patients

There was a trend to show that increasing BMI was associated with higher risk for MetS in patients. Patients with BMI at moderate risk and high risk had adjusted OR for MetS of 5.23 (CI 1.00 to 27.43, $P = 0.050$) and 23.40 (CI 4.44 to 123.20, $P < 0.001$), respectively.

Smoking and MetS in Patients

There was a significantly higher proportion of smokers in the patient group compared to controls. There were more male smokers than female smokers in the patient group ($P < 0.001$). Among those who smoked, a higher proportion in the patient group smoked more than 10 cigarettes a day.

The prevalence of MetS was found to be significantly associated with patients who smoked with an unadjusted OR 2.46 (CI 1.03 to 5.88, $P = 0.042$) compared with patients who did not smoke. The trend suggested that patients who smoked more than 10 cigarettes a day were more associated with MetS. However, after adjusting for BMI, smoking was no longer significantly associated with MetS in patients.

Discussion

The MetS defines a phenotype with increased risk of cardiovascular disease and has important clinical implications in the prevention of related morbidity and mortality. In this study, we found that patients with schizophrenia in Singapore had an almost 3-fold increased prevalence of MetS according to the AHA/NHLBI criteria. Increasing BMI was associated with increased prevalence of MetS, while smoking was not. The prevalence rate of 46.0% of MetS in schizophrenia was within the range of

prevalence rates that had been reported in other published studies.

Our finding that BMI is associated with MetS has important clinical relevance. BMI is an easily obtainable measurement and is routinely measured in most clinical practices. It might inform clinicians of the potential risk of MetS and the consequent risks of cardiovascular morbidity and mortality. Therefore, BMI could be a useful surrogate to screen and monitor for the development of MetS.

Smoking is a well-established risk factor for cardiovascular diseases. Although smoking was no longer significantly associated with MetS after adjustment for BMI, there was still a larger proportion of smokers in the patient sample. This is important as smoking had been shown to be modifiable to reduce the overall risk of cardiovascular events.²¹

One of the strengths of this study was the reliable collection of measurements and fasted venous blood samples in a single site. This reduced potential bias from measurements and laboratory processes. Another strength would be the use of the AHA/NHLBI criterion to classify MetS in the study sample as this criterion had been validated in the local population and found to be most sensitive for prediction of cardiovascular disorder.^{16,22} Therefore, there is clinical utility in subjects discovered to have MetS as this represented significant clinical implications.

The relationship between atypical antipsychotics and metabolic dysregulations had been shown previously, but this study did not reveal significant associations between current antipsychotic prescription and MetS within the patient group.²³ This could be a limitation of the study design not able to detect temporal changes in prescription patterns. Clinicians might have avoided prescribing atypical antipsychotics in patients with metabolic disorders, or switched patients from atypical to typical antipsychotics upon development of related problems. A prospective study design would be preferred to examine the relationship between medications and development of MetS. Other factors such as socioeconomic status, education and exercise could have contributed to the increased prevalence of MetS in patients with schizophrenia. However, we did not have the appropriate data to adjust for these potential confounding factors.

Although inter-ethnic differences in prevalence of MetS has been reported, we did not detect it in this study.²² This is likely due to the relatively small sample of non-Chinese ethnic groups enrolled which resulted in this study not powered to detect this difference.

Conclusion

Our study found a higher prevalence of MetS in patients with schizophrenia, and that increased BMI is a potential risk

factor for MetS in patients. Weight gain forms a component of the BMI calculation and is a highly modifiable risk factor. Therefore, further studies could examine the efficacy and effectiveness of weight-reducing interventions in lowering the risk for MetS and subsequent cardiovascular-related morbidity and mortality in patients with schizophrenia.

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