A 4-Fold Risk of Metabolic Syndrome in Patients With Schizophrenia: The Northern Finland 1966 Birth Cohort Study

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Objective: Schizophrenia is associated with a shortened life expectancy and increased somatic comorbidity with, e.g., cardiovascular disorders. One major risk factor for these disorders is the metabolic syndrome, which has been reported to have a higher frequency in schizophrenic patients. Our objective was to study the prevalence of metabolic syndrome in a population-based birth cohort.

Method: The study sample consisted of 5613 members of the Northern Finland 1966 Birth Cohort who participated in the field study from 1997 to 1998. Subjects were divided into 4 diagnostic categories (DSM-III-R): (1) schizophrenia (N = 31), (2) other functional psychoses (N = 22), (3) nonpsychotic disorders (N = 105), and (4) no psychiatric hospital treatment (N = 5455, comparison group). Subjects were assessed for the presence of metabolic syndrome according to the criteria of the National Cholesterol Education Program.

Results: The prevalence of metabolic syndrome was higher in subjects with schizophrenia compared with the comparison group (19% vs. 6%, p = .010). The prevalence of metabolic syndrome in subjects with other psychoses was 5%. After controlling for sex, the results of logistic regression analysis showed that the risk of metabolic syndrome in schizophrenia was 3.7 (95% CI = 1.5 to 9.0).

Conclusions: The high prevalence of metabolic syndrome in schizophrenia even at such a relatively young age underscores the need to select antipsychotic medications with no or little capability to induce metabolic side effects. Also, developing comprehensive efforts directed at controlling weight and diet and improving physical activity are needed.

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Mortality data of schizophrenic patients reveal that this group has a shortened life span[1]; for example, the life expectancy of a 30-year-old male patient with schizophrenia is about 8 years and for a female about 10 years shorter than in the general population.[2] A meta-analysis concludes that 60% of the excess mortality in patients with schizophrenia is attributable to physical illness.[3] The causes of death comprise a broad range of conditions, similar to the general population, but schizophrenic patients die at a younger age. Mortality from cardiovascular disease is increased in both men and women with schizophrenia.[4] This could partly be due to features of metabolic syndrome, which predispose these patients to developing cardiovascular diseases. Metabolic syndrome, also called *syndrome X*[5] or the *insulin resistance syndrome*,[6] includes 5 major features: (1) abdominal obesity, (2) hypertriglyceridemia, (3) low high-density lipoprotein (HDL) cholesterol, (4) high blood pressure, and (5) high fasting glucose levels.[7] Previous studies of patients with schizophrenia have focused mainly on individual components of metabolic syndrome.

Patients with schizophrenia tend to be obese, and the antipsychotic-related weight gain is well documented in several studies.[8–10] In addition, patients with schizophrenia are likely to have disturbances of glucose[11] and lipid regulation.[12] The elevating effect of antipsychotics on se-

rum lipids is documented in several clinical-based studies involving typical neuroleptics[13,14] and atypical neuroleptics[15–22]—and recently also in one large matched case-control study.[23] Ryan et al.[24] showed that compared with healthy subjects, drug-naive, first-episode patients with schizophrenia had more often impaired fasting glucose tolerance and higher fasting plasma glucose levels. A study with a small number of subjects also suggests that patients with schizophrenia have increased intra-abdominal fat.[25]

In the Northern Finland 1966 Birth Cohort, we have previously found high blood lipid levels in subjects with schizophrenia and other functional psychoses[26] and higher serum triglycerides in early onset schizophrenia[27] in a general population–based birth cohort. We have also reported that the prevalence of hypercholesterolemia, high low-density lipoprotein cholesterol, and hypertriglyceridemia was high in persons using antipsychotic medication compared to persons without such medication.[28]

Recently Heiskanen et al.[29] reported a 2- to 4-fold higher prevalence of metabolic syndrome in long-term schizophrenia outpatients than was previously found in the same area in both men and women. In contrast to previous studies, we investigated the prevalence of metabolic syndrome in subjects with schizophrenia in a general population–based birth cohort. We also studied the prevalence of metabolic syndrome in other psychoses and hospital-treated nonpsychotic psychiatric disorders and contrasted these to cases without psychiatric hospitalization.

METHOD

The Northern Finland 1966 Birth Cohort is an unselected, general-population birth cohort ascertained during midpregnancy, comprising 12,058 live-born children in the provinces of Lapland and Oulu with an expected delivery date during 1966.[30] The study was approved by The Ethics Committee of the Faculty of Medicine of the University of Oulu (Oulu, Finland) and the Ministry of Social Affairs and Health (Helsinki, Finland).

From our study population, 138 had died and 213 were living abroad by 1997 when 8463 cohort members currently living in northern Finland or in the capital area (Helsinki) were invited to participate in a clinical examination. The field study was conducted from 1997 to 1998. For practical reasons, subjects living outside these areas were not invited, and nested sampling was performed. Five thousand six hundred thirteen subjects (66%) participated, gave a written informed consent, had their waist circumference and blood pressure measured, and filled in questionnaires on medication. Blood samples were drawn after overnight fasting. Medication at the time of blood sample was identified by referring to case records in cases of incomplete answers. The doses of antipsychotic medication were converted to chlorpromazine (CPZ) equivalent daily doses according to Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations.[31] Because these recommendations did not include CPZ equivalents of zuclopenthixol, equivalent to 100 mg CPZ to zuclopenthixol 25 mg/day per os and 100 mg/week depot was used.[32]

The subjects were assessed for the presence of metabolic syndrome according to the criteria of the National Cholesterol Education Program.[7] In the presence of 3 or more of the following, the diagnosis of metabolic syndrome was made: abdominal obesity (waist circumference) in men > 102 cm, in women > 88 cm; triglycerides ≥ 150 mg/dL; HDL cholesterol in men < 40 mg/dL, in women < 50 mg/dL; blood pressure ≥ 130/85 mm Hg; and fasting glucose levels ≥ 110 mg/dL. Since nonfasting values differ significantly from fasting values,[33] data from nonfasting blood samples were excluded, and nonfasted subjects were excluded.

The national Finnish Hospital Discharge Register (FHDR) covers all general and mental hospitals. Its coverage and validity have been shown to be acceptable.[34] Diagnoses in the FHDR during the period 1969 to 1986 were coded with the *International Classification of Diseases, Eighth Revision* (ICD-8) classification; from 1987 to 1995, with the ICD-9 along with DSM-III-R criteria;[35] and since January 1, 1996, according to the ICD-10. All cohort members treated at age 16 years or over and appearing in the FHDR until the end of 1997 with FHDR diagnosis number 290 to 309 or 790.20 (ICD-8), 290 to 316 (ICD-9), or F00 to F69 or F99 (ICD-10) were selected. All diagnoses were scrutinized and validated for the DSM-III-R criteria.[36] The final diagnostic categories with DSM-III-R numbers were:

1. Schizophrenia, defined as any individuals who at the time met DSM-III-R criteria (N = 31; 18 men): 295.11 (N = 1), 295.12 (N = 2), 295.30 (N = 2), 295.32 (N = 3), 295.90 (N = 5), 295.91 (N = 2), 295.92 (N = 13), 295.94 (N = 3).
2. Other psychoses, i.e., all functional psychoses except DSM-III-R schizophrenia (N = 22; 11 men): 295.40 (N = 7), 295.70 (N = 2), 296.24 (N = 1), 296.34 (N = 1), 296.44 (N = 4), 297.10 (N = 4), 298.90 (N = 3).
3. Nonpsychotic disorders (N = 105; 67 men): substance use disorders (N = 45), nonpsychotic mood disorders (N = 22), anxiety disorders (N = 15), adjustment disorders (N = 21), personality disorders (N = 18), other nonpsychotic diagnoses (N = 19). Multiple diagnoses were possible; thus, the number of diagnoses exceeds the number of cases.
4. No psychiatric hospital treatment (N = 5455; 2568 men); comparison group.

The significance of differences in proportions was analyzed with Fisher exact test and differences in continuous variables using the Mann-Whitney U test. Logistic regres-

sion analysis was used to estimate the risk for metabolic syndrome between study groups. p Value under .05 was considered statistically significant.

RESULTS

Of all 8463 invited subjects, 5613 (66%) were included in the present study. The rates of nonparticipants in different diagnostic categories were as follows: 58% in the schizophrenia group, 52% in the group of other psychoses, 53% in the group of nonpsychotic disorders, and 32% in the comparison group. In order to evaluate possible selection bias in the groups, we compared sex, age at onset, days at hospital, and number of hospital treatment episodes between participants and nonparticipants. In the nonpsychotic disorders and comparison groups, women participated more often (p = .012 and p = .000, respectively, χ^2 test). There were no other statistically significant differences between the participants and nonparticipants.

The prevalence of metabolic syndrome was 19% in schizophrenia (p = .01 vs. comparison group), 5% in other psychoses, 9% in nonpsychotic disorders, and 6% in the comparison group (Table 1). After adjusting for sex, the results of logistic regression analysis showed that the risk of metabolic syndrome was 3.7 (95% CI = 1.5 to 9.0) in schizophrenia.

The presence of each criterion of metabolic syndrome in different diagnostic groups is presented in Table 2. Schizophrenic subjects had more often abdominal obesity and hypertriglyceridemia compared with the comparison group (p < .001 and p = .001, respectively, Fisher exact test). No other significant differences were found.

Demographic and clinical characteristics (age at onset, days at hospital, number of hospital treatment episodes, and daily dose of antipsychotics) of subjects with schizophrenia in relation to the presence of metabolic syndrome did not differ statistically significantly between groups (data not shown).

Table 1. The Frequency of Metabolic Syndrome in Diagnostic Groups

	Metabolic Syndrome, % (N)		
Diagnostic Group	Yes	No	p Value[a]
Schizophrenia (N = 31)[b]	19.4 (6)	80.6 (25)	.010
Other psychoses (N = 22)[c]	4.5 (1)	95.5 (21)	1.000
Nonpsychotic disorders (N = 105)	8.6 (9)	91.4 (96)	.295
Comparison group (N = 5455)	6.0 (326)	94.0 (5129)	

[a]Fisher exact test testing the difference between each group and comparison group.
[b]Medications were as follows: clozapine, N = 4; risperidone, N = 1; thioridazine, N = 4; perphenazine, N = 2; haloperidol, N = 3; chlorprothixene N = 1; zuclopenthixol, N = 1; chlorpromazine, N = 1; clozapine and haloperidol, N = 1; clozapine and thioridazine, N = 2; risperidone and thioridazine, N = 1; risperidone and chlorpromazine, N = 1; haloperidol and thioridazine, N = 1; perphenazine and thioridazine, N = 2; sulpiride, zuclopenthixol, and levomepromazine, N = 1; 5 persons did not report using any antipsychotic medication.
[c]Medications were as follows: risperidone, N = 1; haloperidol, N = 1; thioridazine, N = 2; perphenazine, N = 2; 16 persons did not report using any antipsychotic medication.

DISCUSSION

Using the National Cholesterol Education Program's definition,[7] we estimated that a fifth (19%) of the schizophrenia patients in their early thirties have metabolic syndrome, whereas the prevalence of metabolic syndrome in the comparison group was 6%. As far as we know, this is the first study reporting the prevalence of metabolic syndrome in schizophrenia in a population-based setting. Studies generally find that schizophrenic patients have elevated mortality rates from natural causes. However, there have been almost no studies of risk factors explaining this excess, and research is urgently needed for identification of specific risk factors.[1] Individuals with metabolic syndrome are at special risk for coronary heart disease. The metabolic syndrome alone predicts about 25% of all new-onset cardiovascular disease, and the presence of metabolic syndrome is also highly predictive of new-onset diabetes.[37] Thus our finding may explain at least part of the excess mortality of schizophrenic patients from cardiovascular disease.

The study has a number of strengths, stemming from its population-based and birth cohort design. The birth cohort design means that the subjects are all the same age, eliminating confounding from this factor, and the population-based design means that the sample is also comparatively free from selection bias. Because there were no differences in the age at onset, days at hospital, and number of hospital treatment sessions between participants and nonparticipants, we think that our sample is representative and reflects the frequency of metabolic syndrome in schizophrenia and other psychoses. Almost all psychotic patients in Finland are sometimes treated in hospital. By contrast, the nonpsychotic disorders are commonly treated outside hospitals, and thus this group in our study may not be representative.

Regarding diagnostic specificity, increased probability of metabolic syndrome was associated with DSM-III-R schizophrenia but not with nonschizophrenic psychoses (although the number of cases was small) or hospital-treated nonpsychotic disorders. This preliminary finding of diagnostic specificity requires replications within larger study samples.

Although patients with schizophrenia are more at risk for abnormal glucose levels than matched controls,[24] in the present study none of the schizophrenia patients or subjects with other psychoses had fasting glucose levels

Table 2. The Presence of Each Criterion of Metabolic Syndrome in Different Diagnostic Groups, % (N)

Criterion	Diagnostic Group			
	Schizophrenia (N = 31)	Other Psychoses (N = 22)	Nonpsychotic Disorders (N = 105)	Comparison Group (N = 5455)
Abdominal obesity	42 (13)	18 (4)	20 (21)	13 (683)
Triglycerides ≥ 150 mg/dL	39 (12)	27 (6)	18 (19)	15 (831)
HDL cholesterol men < 40 mg/dL, women < 50 mg/dL	16 (5)	5 (1)	20 (21)	11 (588)
Blood pressure ≥ 130/85 mm Hg	48 (15)	45 (10)	36 (38)	40 (2209)
Fasting glucose ≥ 110 mg/dL	0 (0)	0 (0)	3 (3)	3 (157)

Abbreviation: HDL = high-density lipoprotein.

greater than or equal to 110 mg/dL. Also, in the other groups only 3% of subjects met the criterion of high fasting glucose levels; hence, this phenomenon may simply reflect the limited number of subjects with psychotic illness in this study. It also brings to the fore the issue that in order to have the metabolic syndrome, one does not need to have impaired fasting glucose tolerance.

In the only previous study of metabolic syndrome in schizophrenia,[29] the prevalence of metabolic syndrome was 37% in long-term schizophrenics with a mean age of 45 years. The lower prevalence (19%) of metabolic syndrome found here may be partly due to younger age of our study group and the increasing prevalence of metabolic syndrome with age.[38] In the previous study,[29] the study sample consisted of 35 long-term schizophrenia patients from the psychiatric rehabilitation ward, having many hospital treatment sessions and hospital days. Compared to that sample, the subjects in the present study seem to have fewer hospital treatment episodes and days at hospital, suggesting that patients with more severe illness might be at higher risk for metabolic syndrome. However, in our study there was no association in relation to the presence of metabolic syndrome in demographic or clinical variables. Further studies in a larger population-based sample are therefore needed to investigate whether the severity of schizophrenia, or daily dose or type of antipsychotic medication, correlates with the incidence of metabolic syndrome.

It is unclear how much of the increased risk of metabolic syndrome in the sample was due to unhealthy lifestyle issues, e.g., poor diet, lack of exercise, and cigarette smoking, which are known to have higher prevalence in schizophrenics than in the general population. Schizophrenia and high blood glucose levels may be linked also independently of medication.[24,39] Although there is some evidence that atypical antipsychotics can cause increased risk of diabetes mellitus,[22] the attributable risk of diabetes mellitus associated with atypical antipsychotics when compared to conventional antipsychotics seems to be small, about 2% for clozapine and less than 1% each for quetiapine, olanzapine, and risperidone.[40] The use of antipsychotics may also partly explain the higher prevalence of metabolic syndrome in schizophrenia. Clinicians should pay attention to the selection of antipsychotic medication, because different antipsychotics seem to have different effects on glucose and lipid levels.[41] There are guidelines for the treatment of psychotic patients with clinically significant obesity[42] and for monitoring of and therapeutic interventions in patients taking second-generation antipsychotics.[41,43–46] Patients should be monitored for the development of significant weight gain, dyslipidemia, and diabetes and treated if these side effects develop.[41,43–46]

The basic causes and mechanisms of the metabolic syndrome are not known, but for the majority of patients, improper nutrition and inadequate physical activity are of importance. Some interventions for managing weight gain associated with atypical antipsychotics have been studied,[47,48] but further studies of interventions and their effectiveness are needed. There is currently very limited evidence available that behavioral interventions actually work in overweight patients treated with antipsychotics.[8] The characteristics of schizophrenia patients mean that management of weight will be even more difficult to achieve than in populations without mental health difficulties. The high prevalence of this syndrome in schizophrenia even at such a young age underscores the need to develop comprehensive efforts directed at controlling weight and improving physical activity and the importance of selecting antipsychotic medications with no or little capability to induce metabolic side effects. Also, regular monitoring of obesity, serum lipid and glucose levels, and blood pressure, thus screening for the possibility of metabolic syndrome in schizophrenia patients, even in early adulthood, is important.

Drug names: chlorpromazine (Sonazine, Thorazine, and others), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), quetiapine (Seroquel), risperidone (Risperdal).

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