Metabolic Syndrome Among Persons With Schizophrenia and Other Psychotic Disorders in a General Population Survey

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Objective: To determine the prevalence of metabolic syndrome and investigate its components in individuals with psychotic disorders and individuals using antipsychotic medication in a general population study.

Method: The study population was a nationally representative, 2-stage cluster sample of 8028 persons aged 30 years or over from Finland. The field work for this study took place between September 2000 and June 2001. Laboratory and other measurements related to metabolic syndrome were taken in a health examination. We used the Structured Clinical Interview for DSM-IV (SCID-I) and case note data when making diagnostic assessments according to DSM-IV-TR criteria. Metabolic syndrome was diagnosed according to Adult Treatment Panel III criteria. Subjects who had not fasted the required 4 hours were excluded from the analysis. Prevalences of metabolic syndrome, adjusting for age, sex, and hours of fasting, were estimated by calculating predicted marginals, evaluated at 8 hours of fasting.

Results: The prevalence estimates of metabolic syndrome were 36.2% (SE = 7.3), 41.4% (SE = 6.3), and 25.0% (SE = 8.6) among subjects with schizophrenia, other nonaffective psychosis, and affective psychosis, respectively, compared with 30.1% (SE = 0.8) in subjects without psychotic disorders. Subjects with schizophrenia had significantly lower high-density lipoprotein cholesterol and higher triglyceride and glucose levels and larger waist circumference, but also lower systolic blood pressure, than the remaining study population (all p values < .05). While all markers of metabolic syndrome were elevated among subjects with other nonaffective psychotic disorders, only the difference in waist circumference was statistically significant ($p < .05$). The prevalence of metabolic syndrome was significantly elevated among users of high-potency (52.1% [SE = 6.6]; $p < .001$) but not low-potency (39.0% [SE = 6.9]) and atypical (23.4% [SE = 10.8]) antipsychotic medication.

Conclusion: Nonaffective psychotic disorders are associated with abdominal obesity and glucose and lipid abnormalities. Regular monitoring and active treatment of metabolic abnormalities are essential in this patient population.

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The term *metabolic syndrome* is used to describe a cluster of variables that together markedly increase the risk of developing type 2 diabetes mellitus and atherosclerotic vascular disease.[1–3] Metabolic syndrome is characterized by glucose homeostasis abnormalities, dyslipidemia, hypertension, and abdominal obesity.[2] Environmental risk factors for metabolic syndrome include sedentary lifestyle and poor physical fitness, a diet rich in saturated fat and low in fiber, low socioeconomic status, and low birth weight and rapid childhood growth, but genetic factors also contribute significantly to its development.[2]

The prevalence of metabolic syndrome among patients with schizophrenia has varied between 19% and 63% using the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III) criteria,[4] being up to 4 times higher than in the general population.[5–12] The difference in prevalence between patients with schizophrenia and the general population has been largest in studies assessing young adults,[7] and the disparity appears to diminish with advancing age.[8,11,12] Most studies on patients

with schizophrenia have found a higher prevalence of metabolic syndrome in females than males.[6–10,12]

Studies concerning other psychotic disorders have been rarer, and results mixed. Some have found an increased risk of metabolic syndrome in patients with other psychotic and severe affective disorders,[13,14] while others have not.[7,15]

Lifestyle-related risk factors for metabolic syndrome, such as low physical activity and unhealthy diet, are common in subjects with psychotic disorders,[16] but antipsychotic medication may confer an additional risk. Whether atypical rather than typical antipsychotic drugs are related to higher risk is unknown,[12,17] since recent studies have usually focused on comparing different atypical antipsychotics rather than comparing typical versus atypical antipsychotics and have usually investigated components of metabolic syndrome rather than the whole syndrome.[18] Antipsychotic drugs may contribute to the development of metabolic syndrome by causing weight gain,[19,20] lipid abnormalities,[18,21] and abnormalities in glucose regulation.[22–27]

The aims of this study were to investigate the prevalence of metabolic syndrome and its components among persons with psychotic disorders and those using antipsychotic medication and to investigate factors associated with metabolic syndrome among persons with psychotic disorders in a general population survey representative of the Finnish adult population.

METHOD

Study Population

The Health 2000 study was based on a nationally representative, 2-stage cluster sample of 8028 persons aged 30 years or over from 80 municipalities or groups of municipalities with joint primary care in Finland, including the 15 biggest towns. Subjects aged 80 years or over were oversampled by doubling their sampling fraction. The field work took place between September 2000 and June 2001 and consisted of a home interview and a health examination at the local health center or a condensed interview and health examination of nonrespondents at home. In addition, register information was gathered on the whole sample. The study was approved by the ethics committee of the Hospital District of Helsinki and Uusimaa, and participants gave written informed consent.[28]

Diagnostic Assessment of Psychotic Disorders

We screened subjects with possible psychotic disorder and interviewed them using the Research Version of the Structured Clinical Interview for DSM-IV-TR (SCID-I).[29] Subjects were screened to participate in the SCID interview if they reported having been diagnosed with a psychotic disorder, having received a diagnosis of possible or definite psychotic disorder from the physician conducting the health examination, or having had possible psychotic or manic symptoms according to the Composite International Diagnostic Interview (World Health Organization, http://www3.who.int/cidi/index.htm) conducted as part of the health examination. A register-based screen was also used, including hospital treatment for a diagnosis of any psychotic disorder, reimbursed antipsychotic medication, disability pension because of psychotic disorder, or mood-stabilizing medication use without a diagnosis of any relevant somatic condition.[30]

There were 700 screen-positive persons alive at the time of our contact, of whom we were able to interview 444 (63.4%) using the SCID.[30] We diagnosed those who did not participate in the SCID interview using hospital and outpatient case notes from psychiatric and primary care units. Case notes for those who participated in the interview were also collected. The final best-estimate diagnoses were made by J.M.S., J.P., and S.I.S. using DSM-IV-TR criteria and were based on all available, systematically evaluated information from the interview and/or case records.[30] Kappa values between the raters ranged from 0.74 to 0.97 for different psychotic disorders.[30] In the present article, lifetime-ever diagnoses of functional psychotic disorders are classified into schizophrenia, other nonaffective psychotic disorder (ONAP) (schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, and psychotic disorder not otherwise specified), and affective psychosis (bipolar I disorder and major depressive disorder with psychotic features).

Diagnosis of Metabolic Syndrome

Metabolic syndrome was diagnosed using the NCEP ATP-III criteria,[4] which require at least 3 of the following to be present: (1) central obesity, defined as waist circumference > 102 cm in men and > 88 cm in women; (2) high fasting triglycerides, defined as ≥ 150 mg/dL; (3) low high-density lipoprotein (HDL) cholesterol, defined as < 40 mg/dL in men and < 50 mg/dL in women; (4) elevated blood pressure, defined as systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg; and (5) impaired fasting glucose, defined as fasting glucose ≥ 110 mg/dL. Only subjects who had fasted at least 4 hours and who had all measurements needed for the assessment of metabolic syndrome were included in the analyses. All measurements related to metabolic syndrome were available for 6530 persons (81.3% of the original study sample), and, of these, 83.2% (N = 5434) had fasted for the required 4 hours.

We also report prevalences using the criteria of the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI),[31] by which criterion 2 was fulfilled if the subject had high fasting triglycerides or used lipid-lowering medication, criterion 4 was ful-

filled if the subject had elevated blood pressure or used antihypertensive medication, and criterion 5 was fulfilled if fasting glucose was ≥ 100 mg/dL or the subject had drug treatment for elevated glucose.[31]

Measurements

Subjects were asked to fast at least 4 hours before the examination, with the exception of subjects with insulin-treated diabetes mellitus. Blood samples were taken at the beginning of the health examination or home health examination. Serum samples were centrifuged and stored in freezers at –70°C. Laboratory analyses were conducted at the National Public Health Institute or at the Social Insurance Institution's research laboratory within 6 months of the health examination.[32]

Total, HDL, and low-density lipoprotein (LDL) cholesterol, triglycerides, and glucose were measured with an Olympus AU400 analyzer (Olympus Optical Ltd., Mishima, Japan). Glucose was measured by a hexokinase method with a between-series coefficient of variation of 2.3%. Total cholesterol, HDL cholesterol, and triglycerides were measured by a photometric enzymatic method, with a between-series coefficient of variation of 2.2%, 5.3%, and 3.2%, respectively. LDL cholesterol was measured by the direct LDL-C Plus assay (Roche Diagnostics, Mannheim, Germany), with a between-series coefficient of variation of 5.7%. Serum insulin concentrations were determined with an Abbott IMx 20238 analyzer (Abbott Diagnostics, Abbott Park, Ill.) by microparticle enzyme immunoassay.[32]

Blood pressure was measured after a 5-minute rest twice from the right upper arm with the person sitting. Values reported here are mean values from the 2 measurements. Weight was measured during bioimpedance measurement. Waist circumference was measured while standing, midway between the lowest rib and the iliac crest, after a modest expiration.[28]

Other Variables

Information on general education and on higher and vocational education was combined into a level-of-education variable (basic, secondary, or higher).[28]

Antipsychotic medications were categorized as low-potency (thioridazine, chlorprotixene, levomepromazine, chlorpromazine, promazine, melperone, sulpiride), high-potency (fluphenazine, haloperidol, flupenthixol, zuclopenthixol, pericyazine, perphenazine), and atypical (clozapine, olanzapine, risperidone, quetiapine). Lipid-lowering medication included statins, fibrates, ezetimibe, colestyramine, and cholestipol. Antidiabetic medication included insulin and oral antidiabetic medication (insulin sensitizers, sulfonylureas, repaglinide, nateglinide, and metformin). Antihypertensive medication included beta blockers, calcium antagonists, diuretics, angiotensin-converting enzyme (ACE) inhibitors, alpha-1 blockers, angiotensin II receptor antagonists, clonidine, and moxonidine.

Healthiness of the diet was a summary variable based on standardized, diet-related questions that assessed the habitual use of butter versus vegetable oils, fat content in milk and cheese products, and daily use of raw vegetables.[28] Diet was coded as healthy (high use of vegetables and low use of saturated fat), average, and unhealthy (low use of vegetables and high use of saturated fat). Smoking status was categorized as current smoker, ex-smoker, and never a regular smoker.[28]

Handgrip strength, measured in the health examination, was used as a measure of physical condition. Low handgrip strength has predicted the development of insulin resistance in previous studies.[33]

Statistical Analysis

All analyses were conducted using SUDAAN, Release 9.0,[34] which is able to take account of 2-stage cluster sampling design and calculates robust standard error estimates. Sampling design was included in all statistical analyses. In addition, poststratification weights estimated by Statistics Finland were applied to adjust for nonresponse and for the oversampling of individuals aged 80 years and over.[28]

Duration of fasting differed between the participants, as some were examined in the morning and others in the afternoon. The mean duration of fasting was 7.9 (95% CI = 6.5 to 9.3) hours in subjects with schizophrenia and 10.6 (95% CI = 9.1 to 12.1), 7.8 (95% CI = 6.3 to 9.4), and 8.5 (95% CI = 8.4 to 8.7) hours in subjects with ONAP, subjects with affective psychosis, and the remaining study population, respectively. Fasting duration particularly affects triglyceride and glucose concentrations.[35] In order to control for the confounding effect of fasting duration, and also of age and sex, we estimated the adjusted prevalences of metabolic syndrome and its components using predicted marginals, which provided us with more comparable results than the crude prevalences.[34] The predicted marginals were evaluated at 8 hours of fasting.

In addition, we compared the mean or frequency of variables related to metabolic syndrome or its risk factors among subjects with psychotic disorders, subjects using antipsychotic medication, and the other participants. Differences were tested using the t test for continuous variables, and the χ^2 test for categorical variables. The 95% confidence intervals for prevalences and proportions were calculated using logit transformation to assure that the confidence limits were between 0% and 100%.[34]

We used logistic regression to further explore the odds of having metabolic syndrome. The analyses were conducted in a stepwise manner. First, adjustments were made for only age and sex. Second, education, healthiness of diet, smoking, handgrip strength, and alcohol consumption were added into the model, and the third step added

Table 1. Demographic Characteristics and Mean Values of Variables Related to Metabolic Syndrome for Fasting Subjects (N = 5434) With and Without Psychotic Disorders[a]

Characteristic	Subjects Without Psychotic Disorder	Subjects With Schizophrenia[b]	Subjects With Other Nonaffective Psychosis[b]	Subjects With Affective Psychosis[b]
Age, y	52.5 (52.1 to 52.9)	53.7 (50.2 to 57.3)	54.6 (51.0 to 58.3)	52.9 (48.6 to 57.2)
Sex, N				
Male	2379	16	20	14
Female	2937	22	34	12
Plasma glucose, mg/dL	98.9 (98.4 to 99.5)	**110.1 (100.2 to 120.2)***	105.2 (96.0 to 114.4)	96.4 (91.7 to 100.9)
≥ 126 mg/dL, %	3.4 (3.0 to 4.0)	18.6 (9.2 to 34.0)	7.9 (3.0 to 18.8)	0.0
110–125 mg/dL, %	10.2 (9.3 to 11.2)	5.3 (1.3 to 19.5)	13.7 (6.0 to 28.3)	19.2 (6.9 to 43.4)
< 110 mg/dL, %	86.4 (85.3 to 87.4)	76.1 (59.8 to 87.2)	78.4 (64.7 to 87.8)	80.8 (56.6 to 93.1)
Total cholesterol, mg/dL	230.5 (229.0 to 232.0)	229.7 (212.7 to 247.1)	234.4 (223.9 to 244.8)	237.1 (222.8 to 251.4)
HDL cholesterol, mg/dL	51.4 (51.0 to 51.7)	**46.3 (42.1 to 50.6)***	50.6 (47.1 to 54.1)	47.5 (42.9 to 52.1)
LDL cholesterol, mg/dL	145.2 (143.6 to 146.7)	140.2 (125.9 to 154.8)	148.6 (137.1 to 160.2)	157.5 (143.2 to 171.8)
Triglycerides, mg/dL	139.8 (137.2 to 142.5)	**178.8 (143.4 to 214.2)***	148.7 (126.5 to 170.8)	138.9 (115.0 to 162.8)
Systolic BP, mm Hg	134.5 (133.6 to 135.4)	**127.2 (121.5 to 132.9)***	132.0 (126.7 to 137.3)	**126.1 (118.8 to 133.5)***
Diastolic BP, mm Hg	82.1 (81.5 to 82.7)	79.7 (76.5 to 83.0)	83.5 (80.5 to 86.5)	80.2 (75.9 to 84.4)
BMI, kg/m^2	27.0 (26.9 to 27.1)	27.8 (26.2 to 29.4)	**28.6 (27.2 to 30.0)***	27.4 (25.9 to 28.8)
Waist circumference, cm	92.9 (92.5 to 93.3)	**97.9 (93.1 to 102.7)***	**96.8 (92.9 to 100.7)***	96.6 (91.6 to 101.7)
Antipsychotic medication, %				
Low-potency	0.48 (0.32 to 0.72)	**45.5 (31.6 to 60.1)*****	**22.3 (13.1 to 35.4)****	**20.2 (8.9 to 39.8)****
High-potency	0.28 (0.17 to 0.46)	**44.9 (29.7 to 61.1)*****	**32.4 (21.3 to 43.6)*****	12.3 (4.1 to 31.5)
Atypical	0.06 (0.02 to 0.16)	**17.6 (8.4 to 33.3)****	**7.4 (2.8 to 18.2)***	0.0
Any	0.79 (0.58 to 1.10)	**73.2 (57.6 to 84.6)*****	**47.2 (17.1 to 32.4)*****	**32.5 (15.9 to 55.1)****
Antidiabetic medication, %	1.7 (1.4 to 2.0)	7.7 (2.5 to 21.3)	2.0 (0.3 to 12.8)	0.0
Lipid-lowering medication, %	6.0 (5.3 to 6.8)	2.8 (0.4 to 17.2)	1.9 (0.3 to 12.2)	0.0
Antihypertensive drug use, %	23.4 (22.3 to 24.6)	26.7 (15.7 to 41.5)	29.8 (20.0 to 41.9)	19.9 (8.3 to 40.6)
Education, %				
Highest	28.2 (26.9 to 29.6)	15.8 (7.1 to 31.5)	22.0 (13.5 to 33.8)	42.1 (23.8 to 63.0)
Middle	32.3 (31.1 to 33.5)	23.8 (13.2 to 39.1)	24.5 (14.2 to 38.8)	16.3 (6.9 to 33.9)
Lowest	39.5 (38.0 to 41.1)	60.4 (44.6 to 74.3)	53.6 (40.8 to 65.9)	41.6 (25.5 to 59.7)
Smoking status, %				
Current	26.7 (25.5 to 27.8)	45.7 (30.9 to 61.2)	35.0 (24.5 to 47.2)	24.6 (11.7 to 44.6)
Previous	22.4 (21.4 to 23.4)	13.5 (5.8 to 28.3)	18.6 (10.2 to 31.5)	27.8 (13.7 to 48.1)
Never	51.0 (49.6 to 52.4)	40.9 (27.4 to 55.9)	46.4 (34.8 to 58.4)	47.6 (30.5 to 65.3)
Diet, %				
Healthy	23.5 (22.2 to 24.9)	12.1 (4.7 to 27.6)	19.1 (10.6 to 31.9)	26.7 (14.1 to 44.7)
Average	62.5 (61.3 to 63.7)	67.6 (51.1 to 80.6)	69.5 (55.7 to 80.5)	54.0 (36.4 to 70.7)
Unhealthy	14.0 (12.9 to 15.2)	20.3 (10.0 to 36.9)	11.5 (5.0 to 24.0)	19.3 (7.9 to 40.0)
Handgrip strength, newtons	373.2 (369.2 to 377.2)	**297.3 (263.6 to 331.0)*****	343.1 (296.9 to 389.2)	367.6 (317.0 to 418.2)
Alcohol consumption, g/wk	78.5 (73.3 to 83.7)	**23.2 (0.0 to 47.8)*****	85.5 (49.6 to 121.5)	74.2 (27.5 to 120.8)

[a]95% confidence intervals are shown in parentheses.
[b]Significant values (in contrast to other participants) are shown in boldface: *p < .05, **p < .01, ***p < .001.
Abbreviations: BMI = body mass index, BP = blood pressure, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

antipsychotic medications. Schizophrenia, ONAP, and affective psychoses were modeled separately.

RESULTS

Prevalence and Components of Metabolic Syndrome in Subjects With Psychotic Disorder

Subjects with psychotic disorders had complied with fasting instructions less often than the other participants. The proportion of subjects who had fasted at least 4 hours was 81.9% in the total sample and 70.6%, 77.5%, and 65.5% among subjects with schizophrenia, ONAP, and affective psychosis, respectively.

Subjects with schizophrenia had significantly higher fasting plasma glucose and triglyceride levels, lower HDL cholesterol level, and larger waist circumference, but also lower systolic blood pressure, than the rest of the study population. Subjects with ONAP had larger waist circumference and higher body mass index, while subjects with affective psychoses had lower systolic blood pressure (Table 1).

The prevalence estimates of metabolic syndrome were 36.2% (SE = 7.3), 41.4% (SE = 6.3), and 25.0% (SE = 8.6) among subjects with schizophrenia, ONAP, and affective psychosis, respectively, compared with 30.1% (SE = 0.8) in subjects without psychotic disorders (Table 2). Among subjects with schizophrenia and ONAP, the prevalence of metabolic syndrome was high already in the age group 30–54 years but did not differ from the rest of the sample aged 55 years and over (Table 2). The ONAP group mainly consisted of subjects with schizoaffective disorder, delusional disorder, and psychotic disorder not otherwise specified, and the estimated prevalences of metabolic syndrome in these groups were 61.8% (SE = 13.6),

Table 2. Prevalence of Metabolic Syndrome According to the Adult Treatment Panel III Criteria in Subjects With Psychotic Disorders and in the Total Study Sample[a]

Characteristic	Total Sample	Subjects With Schizophrenia[b]	Subjects With Other Nonaffective Psychosis[b]	Subjects With Affective Psychosis
Total[c]	30.1 (0.8)	36.2 (7.3)	41.4 (6.3)	25.0 (8.6)
Sex[d]				
Male	29.7 (1.0)	29.8 (11.9)	42.8 (9.2)	25.4 (11.7)
Female	30.5 (1.0)	41.5 (10.0)	40.3 (8.4)	25.7 (11.7)
Age[e]				
30–54 y	22.1 (0.9)	37.6 (10.6)	**47.2 (8.8)*****	19.4 (10.3)
≥ 55 y	42.1 (1.3)	38.0 (11.4)	40.0 (9.3)	36.5 (15.4)
Prevalence of the components of metabolic syndrome				
Impaired fasting glucose	13.1 (0.5)	23.7 (6.8)	19.0 (5.5)	19.3 (9.7)
Elevated blood pressure	61.5 (1.0)	**41.7 (7.2)****	69.1 (5.2)	44.8 (10.8)
Hypertriglyceridemia	32.6 (0.7)	**46.2 (7.2)***	36.8 (6.4)	20.6 (7.7)
Low HDL cholesterol	33.8 (0.9)	**50.8 (8.5)***	34.1 (6.0)	44.9 (9.4)
Abdominal obesity	39.8 (0.7)	51.5 (7.7)	**58.7 (6.1)****	44.5 (10.3)

[a]Prevalence values are shown as % (SE).
[b]Significant values (in contrast to other participants) are shown in boldface: *p < .05, **p < .01, ***p < .001.
[c]Adjusted for age, sex, and hours of fasting.
[d]Adjusted for age and hours of fasting.
[e]Adjusted for sex and hours of fasting.
Abbreviation: HDL = high-density lipoprotein.

Table 3. Number of Adult Treatment Panel III Criteria for Metabolic Syndrome Met by Subjects With Psychotic Disorders and Subjects Using Antipsychotic Medication[a]

	Number of Criteria Met for Metabolic Syndrome					
Subject Group	0	1	2	3	4	5
Schizophrenia	10.9 (4.3 to 25.2)	24.1 (12.8 to 40.7)	22.5 (11.8 to 38.7)	15.4 (7.3 to 29.7)	16.6 (7.6 to 32.2)	10.5 (4.1 to 24.7)
Other nonaffective psychosis	11.4 (5.3 to 22.7)	18.4 (10.2 to 30.7)	23.6 (13.4 to 38.1)	18.4 (9.9 to 31.8)	24.4 (14.5 to 37.9)	3.9 (1.0 to 13.8)
Affective psychosis	19.7 (8.6 to 38.8)	16.9 (6.4 to 37.6)	34.7 (18.7 to 55.2)	15.0 (5.5 to 34.9)	13.8 (5.0 to 32.7)	0.0
High-potency antipsychotic users	6.2 (2.1 to 17.0)	18.5 (9.8 to 32.3)	14.7 (7.1 to 27.9)	26.8 (16.6 to 40.2)	27.3 (17.5 to 39.9)	6.5 (2.2 to 17.8)
Low-potency antipsychotic users	9.1 (3.8 to 20.1)	16.2 (8.5 to 28.8)	24.2 (14.6 to 37.4)	26.8 (16.4 to 40.6)	20.2 (10.7 to 34.7)	3.5 (1.0 to 12.1)
Atypical antipsychotic users	39.4 (17.4 to 66.8)	7.9 (1.1 to 40.5)	24.5 (8.2 to 54.0)	16.2 (4.1 to 46.4)	7.1 (1.0 to 37.6)	5.0 (0.7 to 29.2)
Total sample	17.8 (16.7 to 19.0)	26.3 (25.0 to 27.6)	23.5 (22.4 to 24.6)	17.7 (16.7 to 18.8)	11.2 (10.3 to 12.1)	3.5 (3.0 to 4.1)

[a]Values are shown as % (95% CI).

44.7% (SE = 15.5), and 30.4% (SE = 8.4), the difference between subjects with schizoaffective disorder and the total sample being statistically significant (adjusted F = 5.32, df = 1, p = .02).

When components of metabolic syndrome were dichotomized according to whether each individual criterion of metabolic syndrome was met or not, the criteria related to hypertriglyceridemia and low HDL cholesterol were met significantly more often, and the criterion related to elevated blood pressure, less often, in subjects with schizophrenia (Table 2). Subjects with ONAP met the criterion for abdominal obesity more often (Table 2). There was an overall tendency among subjects with schizophrenia and ONAP to meet more criteria of metabolic syndrome than the overall study population (Table 3). The mean number of criteria met for metabolic syndrome was 1.88 (95% CI = 1.83 to 1.92) in subjects without psychotic disorders and was significantly higher in subjects with schizophrenia (2.34, 95% CI = 1.89 to 2.79, p = .049) and ONAP (2.38, 95% CI = 2.05 to 2.71, p = .003), but not in subjects with affective psychosis (1.86, 95% CI = 1.37 to 2.36, p = .92).

Subjects with schizophrenia and ONAP used antidiabetic and antihypertensive medication more often and lipid-lowering medication less often than the other members of the study population, while subjects with affective psychosis used all these medications less often. When we used the AHA/NHLBI criteria for metabolic syndrome, its estimated prevalence rose to 38.1% (SE = 0.8) in the total population and to 47.1% (SE = 7.9), 51.1% (SE = 6.5), and 33.0% (SE = 8.9) in subjects with schizophrenia, ONAP, and affective psychosis, respectively, the difference between the ONAP group and the remaining study population being statistically significant (adjusted F = 4.15, p = .042). AHA/NHLBI's criterion for impaired fasting glucose was fulfilled by 34.5% (SE = 0.7) in

Table 4. Demographic Characteristics and Mean Values of Variables Related to Metabolic Syndrome for Fasting Subjects Who Used Antipsychotic Medication and for Whom All Information Required for Diagnosis of Metabolic Syndrome Was Available[a,b]

Characteristic	Class of Antipsychotic Medication		
	High-Potency	Low-Potency	Atypical
Age, y	55.5 (52.2 to 58.8)	**56.7 (53.4 to 60.1)***	57.6 (50.7 to 64.5)
Sex, N			
Male	24	29	5
Female	29	36	10
Functional psychosis, N			
Yes	37	34	11
No	16	31	4
BMI, kg/m^2	**29.6 (28.1 to 31.1)*****	27.6 (26.2 to 29.0)	27.1 (24.8 to 29.4)
Waist circumference, cm	**101.7 (97.3 to 106.0)*****	**97.3 (93.3 to 101.2)***	92.7 (86.0 to 99.3)
Mean blood glucose, mg/dL	105.4 (96.8 to 114.2)	107.0 (98.7 to 115.3)	103.4 (91.0 to 115.7)
≥ 126 mg/dL, %	12.1 (5.6 to 24.1)	11.3 (5.1 to 23.5)	12.3 (2.9 to 39.7)
110–125 mg/dL, %	13.9 (7.0 to 25.9)	17.2 (9.7 to 28.6)	0.0
< 110 mg/dL, %	74.0 (60.0 to 84.4)	71.5 (59.6 to 81.0)	87.7 (60.3 to 97.1)
Total cholesterol, mg/dL	234.7 (222.0 to 247.5)	227.0 (214.7 to 239.0)	**207.7 (190.3 to 225.5)***
HDL cholesterol, mg/dL	**46.3 (42.9 to 50.2)****	**44.8 (42.5 to 47.1)*****	47.1 (40.9 to 53.7)
LDL cholesterol, mg/dL	150.2 (138.2 to 162.5)	144.4 (134.0 to 155.2)	**122.4 (107.3 to 137.8)****
Triglycerides, mg/dL	**165.5 (142.5 to 188.5)***	165.5 (138.9 to 192.9)	155.8 (111.5 to 200.0)
Systolic BP, mm Hg	134.7 (129.3 to 140.3)	**126.0 (119.4 to 132.5)***	**118.3 (110.2 to 126.5)*****
Diastolic BP, mm Hg	**86.2 (83.6 to 88.7)****	**77.6 (74.7 to 80.6)****	**73.1 (67.3 to 78.9)****

[a]95% confidence intervals are shown in parentheses.
[b]Significant values (in contrast to other participants) are shown in boldface: *p < .05, **p < .01, ***p < .001.
Abbreviations: BMI = body mass index, BP = blood pressure, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

the general population, and by 55.0% (SE = 9.1), 46.0% (SE = 6.8), and 28.3% (SE = 9.0) of subjects with schizophrenia, ONAP, and affective psychosis, respectively. The differences between subjects with schizophrenia (F = 5.0, p = .025) and ONAP (F = 4.51, p = .03) and the remaining study population were statistically significant.

Prevalence and Components of Metabolic Syndrome in Subjects Using Antipsychotic Medication

Of subjects using high-potency antipsychotic medication, 74.9% had fasted at least 4 hours, and the respective proportions were 67.3% and 58.8% for users of low-potency and atypical antipsychotics. Subjects who used low-potency antipsychotic medication were older than the remaining study population, but there were no significant gender differences. A diagnosis of functional psychotic disorder was least common among users of low-potency antipsychotic medication. Use of atypical antipsychotic medication was rare, and most subjects (11 out of 15) used risperidone (Table 4).

The estimated prevalence of metabolic syndrome was significantly higher than in the total sample among users of high-potency (52.1% [SE = 6.6]) but not low-potency (39.0% [SE = 6.9]) and atypical (23.4% [SE = 10.8]) antipsychotic medication (Table 5). The prevalence of metabolic syndrome was high already in the 30–54-year age group among users of high- and low-potency antipsychotic medication, while the prevalence among those aged 55 years or more no longer differed significantly from the general population (Table 5).

Subjects who used high-potency antipsychotic medication had significantly higher triglyceride and lower HDL cholesterol levels, larger waist circumference, and higher diastolic blood pressure than the other participants (Table 4), and they met the criteria for hypertriglyceridemia and abdominal obesity more often than the other participants (Table 5). Users of low-potency antipsychotic medication had significantly lower HDL cholesterol concentration and larger waist circumference, but also lower systolic and diastolic blood pressure, than the other participants (Table 4). They met more often than the other participants all criteria for metabolic syndrome except elevated blood pressure, which they met less often (Table 5). There were only 15 subjects who used atypical antipsychotic medication for whom all measures related to metabolic syndrome were available and who had been fasting at least 4 hours. These subjects had significantly lower systolic and diastolic blood pressure than the other participants (Table 4). The mean number of criteria met for metabolic syndrome was significantly higher, compared with the remaining study sample, among subjects using high-potency (2.70, 95% CI = 2.33 to 3.07, p < .0001) and low-potency (2.43, 95% CI = 2.05 to 2.82, p = .006) antipsychotic medication, but not among users of atypical antipsychotics (1.58, 95% CI = 0.77 to 2.39, p = .46).

When the AHA/NHLBI criteria for metabolic syndrome were used, the prevalence of metabolic syndrome rose to 60.0% (SE = 6.7), 53.4% (SE = 7.2), and 33.9% (SE = 14.1) among subjects using high-potency, low-potency, and atypical antipsychotic medication, respec-

Table 5. Prevalence of Metabolic Syndrome in Subjects Using Antipsychotic Medication[a,b]

Characteristic	Class of Antipsychotic Medication		
	High-Potency	Low-Potency	Atypical
Total[c]	**52.1 (6.6)*****	39.0 (6.9)	23.4 (10.8)
Sex[d]			
Male	**58.7 (10.9)****	38.4 (9.2)	20.8 (17.3)
Female	**47.9 (9.1)***	40.0 (9.8)	23.6 (13.8)
Age[e]			
30–54 y	**57.0 (8.8)*****	**43.3 (10.0)***	28.8 (18.1)
≥ 55 y	53.3 (10.2)	38.6 (9.0)	24.6 (16.1)
Prevalence of the components of metabolic syndrome			
Impaired fasting glucose	22.6 (6.0)	**25.0 (5.0)****	11.2 (7.1)
Elevated blood pressure	65.2 (6.2)	**41.2 (6.3)****	**23.5 (11.2)****
Hypertriglyceridemia	**50.6 (6.4)****	**47.1 (7.8)***	32.9 (12.4)
Low HDL cholesterol	41.7 (7.4)	**46.7 (5.9)***	31.9 (12.2)
Abdominal obesity	**67.2 (6.5)*****	**53.3 (5.9)***	38.5 (12.1)

[a]Prevalence values are shown as % (SE).
[b]Significant values (in contrast to other participants) are shown in boldface: *p < .05, **p < .01, ***p < .001.
[c]Adjusted for age, sex, and hours of fasting.
[d]Adjusted for age and hours of fasting.
[e]Adjusted for sex and hours of fasting.
Abbreviation: HDL = high-density lipoprotein.

Table 6. Logistic Regression Analysis of Factors Affecting the Odds of Having Metabolic Syndrome in Subjects With Psychotic Disorder

Variables	Schizophrenia, OR (95% CI)	ONAP, OR (95% CI)	Affective Psychosis, OR (95% CI)
NCEP ATP-III criteria			
Age, sex	1.33 (0.69 to 2.56)	**1.72 (1.00 to 2.96)***	0.75 (0.29 to 1.92)
Age, sex, education, smoking, alcohol use, diet, handgrip strength	1.89 (0.95 to 3.73)	1.75 (0.96 to 3.19)	0.88 (0.32 to 2.42)
Age, sex, education, smoking, alcohol use, diet, handgrip strength, and high-potency, low-potency, and atypical antipsychotic use	0.99 (0.42 to 2.37)	1.08 (0.57 to 2.07)	0.70 (0.24 to 2.11)
AHA/NHLBI criteria			
Age, sex	1.48 (0.75 to 2.93)	**1.85 (1.05 to 3.24)***	0.76 (0.32 to 1.80)
Age, sex, education, smoking, alcohol use, diet, handgrip strength	1.91 (0.94 to 3.87)	1.59 (0.86 to 2.93)	0.91 (0.34 to 2.39)
Age, sex, education, smoking, alcohol use, diet, handgrip strength, and high-potency, low-potency, and atypical antipsychotic use	1.03 (0.42 to 2.51)	1.02 (0.54 to 1.91)	0.70 (0.24 to 1.98)

*p < .05.
Abbreviations: AHA/NHLBI = American Heart Association/National Heart, Lung, and Blood Institute; NCEP ATP-III = National Cholesterol Education Program Adult Treatment Panel III; ONAP = other nonaffective psychosis.

tively. Differences between subjects using high-potency (F = 10.2, p = .0014) and low-potency (F = 4.51, p = .034) antipsychotic medication and the remaining study population were statistically significant.

Logistic Regression Analysis of Variables Related to Metabolic Syndrome

After adjusting for age and gender, only subjects with ONAP had significantly higher odds of having metabolic syndrome (Table 6). When lifestyle-related variables were entered into the model, the effect of schizophrenia became more marked, but the effect of both schizophrenia and ONAP disappeared in the final model that also included medications. Affective psychosis was consistently associated with statistically nonsignificantly lower odds of having metabolic syndrome. In the final model, advanced age, female sex, unhealthy diet, low level of education, low handgrip strength, and high-potency antipsychotic medication (OR = 3.91, 95% CI = 1.68 to 9.11) remained significant predictors of having metabolic syndrome. When the AHA/NHLBI criteria were used, the initial association between metabolic syndrome and schizophrenia and ONAP strengthened slightly, but the results remained otherwise essentially unchanged (Table 6).

Effect of Fasting

Subjects with psychotic disorders and users of antipsychotic medication had fasted less often than other mem-

bers of the study population. Among the nonfasting subjects, the prevalences of metabolic syndrome according to the ATP-III criteria, based on their nonfasting values, were 42.2% (SE = 12.0), 62.5% (SE = 14.1), and 30.0% (SE = 13.4) among subjects with schizophrenia, ONAP, and affective psychosis, respectively, and 26.3% (SE = 7.4), 54.5% (SE = 7.9), and 42.3% (SE = 18.9) among users of high-potency, low-potency, and atypical antipsychotics, respectively, compared with 35.1% (SE = 1.6) in subjects without psychotic disorders.

DISCUSSION

This is the first study that reports the prevalence of metabolic syndrome and its components in subjects with DSM-IV psychotic disorders from a general population survey that is representative of the adult population in 1 country. We found a high prevalence of metabolic syndrome among subjects with nonaffective but not affective psychotic disorders, but the difference compared to the population without psychotic disorders was not as large as some previous studies have suggested. Subjects with nonaffective psychotic disorders in the age group 30–54 years had higher prevalence of metabolic syndrome than the remaining study sample, but in the older age groups, the prevalence of metabolic syndrome was similar in subjects with nonaffective psychotic disorders and other members of the study population. We also showed that use of typical antipsychotic medications is associated with high prevalence of metabolic syndrome.

The prevalence of metabolic syndrome among subjects with schizophrenia in our general population study was in the same range as in previous clinical studies.[5,6,8–12] As in most previous studies, the prevalence of metabolic syndrome was higher among females than males with schizophrenia.[8–11] Schizophrenia was associated with increased prevalence of the central metabolic syndrome features—impaired glucose tolerance, dyslipidemia, and abdominal obesity—but not with increased prevalence of elevated blood pressure, a finding consistent with some,[8,14] but not all,[9,11,12] studies. In fact, the actual prevalence of elevated blood pressure in our study was comparable to that found in, e.g., the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study,[11] but elevated blood pressure was even more prevalent in subjects without psychotic disorders.

Lipid abnormalities and abdominal obesity were most markedly associated with schizophrenia, consistent with many previous studies.[5,7,11,12,36] Of note is that total and LDL cholesterol levels were not elevated, whereas HDL cholesterol was low and triglycerides were elevated. Guidelines for monitoring and treating lipid abnormalities often focus on elevated LDL levels,[37] but low HDL is as important a risk factor for coronary heart disease as is high LDL.[38] Also, hypertriglyceridemia is an independent predictor of cardiovascular disease.[39] In addition, a high triglyceride and low HDL cholesterol concentration is a strong indicator of insulin resistance.[40] Thus, active monitoring of not only total and LDL cholesterol levels but also HDL cholesterol and triglyceride levels is essential in patients with schizophrenia.

Unexpectedly, the prevalence of metabolic syndrome was even higher in subjects with other nonaffective psychotic disorders than in those with schizophrenia. As in subjects with schizophrenia, metabolic syndrome was particularly prevalent in younger subjects with ONAP and was particularly common among subjects with schizoaffective disorder. One previous study by Basu et al.[13] examined metabolic syndrome in subjects with schizoaffective disorder. The mean age of subjects in their study was 46.9 years, and 42.4% had metabolic syndrome. Abdominal obesity, high triglycerides, and elevated blood pressure were the most common abnormalities in their study sample,[13] which accords with our findings concerning the entire ONAP group. Two previous studies[14,41] have investigated medical comorbidity in schizoaffective disorder; one found no difference in medical comorbidity between patients with schizoaffective disorder and schizophrenia,[14] and the other found that subjects with schizoaffective disorder had higher mortality than those with schizophrenia,[41] suggesting that somatic comorbidity may be a particular concern in this patient group. Our sample was too small for assessing the possible role of concurrent antipsychotic and mood-stabilizing medication use, which in a previous study was associated with higher frequency of metabolic abnormalities.[42]

The small group of subjects with affective psychoses, of whom 8 had bipolar I disorder and 18 had major depressive disorder with psychotic features, did not have higher prevalence of metabolic syndrome, which accords with findings by Fagiolini et al.[15] on bipolar I disorder patients, but not with Susce et al.,[14] who found no difference in the prevalence of components of metabolic syndrome among subjects with affective disorders and schizophrenia. Nevertheless, these subjects with affective psychoses had a tendency toward lower HDL and higher LDL levels and larger waist circumference than the rest of the study population, consistent with previous studies showing that obesity and dyslipidemias are common health problems among subjects with bipolar I disorder.[14,15,43,44] However, lowered cholesterol levels in patients with bipolar disorder have also been reported.[45] Although previous studies have suggested that bipolar I disorder may be associated with hypertension,[44] we found lower systolic blood pressure in subjects with affective psychosis compared with our total sample. However, the actual mean systolic and diastolic blood pressure measurements in this group with affective psychoses were comparable to those found in Holland by Klumpers et al.,[44] whereas hypertension was more common in the Finnish than the Dutch general population.

Although our results suggest that antipsychotic medication, particularly high-potency antipsychotics, may contribute to the excess morbidity of metabolic syndrome in subjects with nonaffective psychotic disorders, our findings should be interpreted with caution, since we had only cross-sectional information on their use, and the dosage was not recorded. All the depot antipsychotic medications available at the time of the study were the high-potency type. In a previous study, the prevalence of clinically significant obesity was over 4 times higher in subjects using depot antipsychotics compared with the general population,[46] and users of high-potency antipsychotics in our study had the highest BMI and waist circumference. On the other hand, 77 percent of our users of atypical antipsychotics used risperidone, which causes less weight gain[19,20] and dyslipidemia[18,21] than olanzapine and clozapine, although it was associated with type 2 diabetes in our previous study (J.M.S., J.P., S.I.S., et al., manuscript submitted). Nevertheless, our study suggests that metabolic syndrome is common among users of typical antipsychotics, which implies that they should not be considered safer than atypical antipsychotics in their metabolic risk factor profile until studied further. Previous studies have not been able to show this association between metabolic syndrome and typical antipsychotics consistently because atypical antipsychotics are usually compared with haloperidol, which induces less weight gain[19] and, moreover, in our study sample, was associated with only marginally elevated prevalence of metabolic syndrome (40.3%, SE = 15.4). Another recent cross-sectional study limited to patients with schizophrenia also found that with the exception of clozapine, the prevalence of metabolic syndrome among users of all classes of antipsychotic medication was remarkably similar.[12]

Our study results are alarming. Metabolic syndrome markedly increases the risk of coronary heart disease, stroke, and type 2 diabetes,[1,3,47–49] and the high rate of smoking among patients with psychotic illness further increases their risk of developing coronary heart disease.[8,50] A follow-up study from Great Britain found that the probability of developing coronary heart disease or type 2 diabetes over 20 years increased from 11.9% among subjects with no abnormalities related to metabolic syndrome to 40.8% among those with 4 or 5 abnormalities.[3] In our study, about 28% of subjects with nonaffective psychotic disorders had 4 or 5 abnormalities related to metabolic syndrome compared with 14.6% of all participants, suggesting that subjects with nonaffective psychotic disorders are at considerably increased risk of developing coronary heart disease and type 2 diabetes. Metabolic syndrome increases the risk of death in patients with coronary heart disease,[51] and previous studies have found a 1.5- to 3-fold risk of premature death from cardiovascular diseases in subjects with schizophrenia[39,52,53] and affective disorders,[54,55] and among long-stay psychiatric patients in general.[56] The high prevalence of metabolic syndrome among subjects with schizophrenia and other nonaffective psychotic disorders probably contributes to the high mortality. It is also possible that the lack of difference in the prevalence of metabolic syndrome in older subjects with nonaffective psychotic disorders is due to a healthy-survivor effect, as has been suggested.[36]

Interventions consisting of dietary counseling and guidance on increasing the level of physical activity among subjects with impaired glucose tolerance have been shown to ameliorate all abnormalities related to metabolic syndrome and decrease the risk of developing type 2 diabetes.[2,57] Behavioral therapy for treating obesity in patients with schizophrenia and schizoaffective disorder has also been successful.[58] We found that dyslipidemias, in particular, are undertreated among subjects with psychotic disorders, suggesting that medical treatment of metabolic syndrome should also be more active. Guidelines for monitoring and treating obesity, lipid abnormalities, hypertension, and type 2 diabetes in patients with schizophrenia have recently been published.[35,59] Psychiatrists should be active in their efforts to prevent and treat metabolic syndrome and its components.

Considering that our study sample did not include young adults, the prevalence of metabolic syndrome in the total sample was quite comparable to the National Health and Nutrition Examination Survey (NHANES) 1999–2000 findings.[60] Even higher prevalences have been observed in some other populations.[61] Thus, the high prevalence of metabolic syndrome in this general population should not limit the generalizability of our findings. However, elevated blood pressure was more common in the Finnish general population than in many other studies,[49] which partly explains the lack of association between elevated blood pressure and psychotic disorders. Another limitation was that information on diet was based on self-report, and there may have been response bias affecting the results of the regression analyses. Finally, although the study was based on a large general population survey, the number of cases with psychotic disorder was still relatively small, which limited our statistical power.

Subjects with psychotic disorders and users of antipsychotic medication had complied with instructions concerning fasting less often than other participants. There were more subjects with type 2 diabetes in these groups (J.M.S., J.P., S.I.S., et al., manuscript submitted), which may be 1 reason for their lesser compliance with fasting instructions. Based on nonfasting values, metabolic syndrome was particularly common among subjects with schizophrenia and ONAP and users of low-potency and atypical antipsychotics who had not fasted and were therefore excluded from the analyses. Thus, the reported prevalences in these groups were underestimations.

CONCLUSIONS

Glucose and lipid abnormalities and abdominal obesity are common in subjects with nonaffective psychotic disorders, while subjects with affective psychoses may not differ from the general population in the prevalence of metabolic syndrome or its components. Use of typical antipsychotics is associated with increased prevalence of metabolic syndrome. Regular monitoring of weight and glucose and lipid values is essential in subjects with psychotic disorders and also in subjects using antipsychotic medication, regardless of the indication.

Drug names: chlorpromazine (Sonazine, Thorazine, and others), clonidine (Catapres, Duraclon, and others), clozapine (Clozaril, FazaClo, and others), ezetimibe (Zetia), fluphenazine (Prolixin and others), haloperidol (Haldol and others), metformin (Glucophage, Glumetza, and others), nateglinide (Starlix), olanzapine (Zyprexa), quetiapine (Seroquel), repaglinide (Prandin), risperidone (Risperdal).

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