Metabolic Syndrome and the Risk of Coronary Heart Disease in 367 Patients Treated With Second-Generation Antipsychotic Drugs

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Objective: To examine the relationship between presence of metabolic syndrome and the risk of coronary heart disease (CHD) events (angina pectoris, myocardial infarction, and sudden cardiac death) in patients treated with second-generation antipsychotic medications.

Method: 367 adults treated with second-generation antipsychotics randomly selected from consecutive psychiatric admissions to a single hospital between August 1, 2004, and March 1, 2005, underwent assessments evaluating the presence of metabolic syndrome. The 10-year risk of CHD events was calculated according to the Framingham scoring system for age, smoking, total cholesterol, high-density lipoprotein (HDL)-cholesterol, blood pressure, and history of diabetes and was compared in patients with and without the metabolic syndrome.

Results: Metabolic syndrome, present in 137 patients (37.3%), was associated with a significantly greater age- and race-adjusted 10-year risk of CHD events, i.e., 11.5% vs. 5.3% for men (risk ratio = 2.18, 95% CI = 1.88 to 2.48, $p < .0001$) and 4.5% vs. 2.3% for women (risk ratio = 1.94, 95% CI = 1.65 to 2.23, $p = .0005$). The increased risk of CHD events in patients with metabolic syndrome remained significant after the exclusion of diabetic patients. In a logistic regression analysis of variables independent of the Framingham scoring system, triglyceride levels ($p < .0001$), waist circumference ($p = .035$), and white race ($p = .047$) were significantly associated with the 10-year risk of CHD events ($R^2 = 0.134$; $p < .0001$).

Conclusions: These data confirm the high prevalence of metabolic syndrome in patients receiving second-generation antipsychotics, indicate that metabolic syndrome doubles the 10-year risk of CHD events in this population, and emphasize the importance of the "hypertriglyceridemic waist" for the identification of psychiatric patients at high risk of CHD.

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In 2001, the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults defined metabolic syndrome as a condition that includes 3 or more of the following 5 characteristics: abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL)-cholesterol, high blood pressure, and high fasting glucose.[1] The metabolic syndrome reflects insulin resistance and atherogenic dyslipidemia; its major consequences are type 2 diabetes mellitus and cardiovascular disease.[2]

The age-adjusted and unadjusted prevalences of metabolic syndrome as defined by NCEP in the United States are 23.7% and 21.8%, being similar in men and women.[3] Community studies using the Framingham model to assess the risk of coronary heart disease (CHD) events by scoring age, smoking, total cholesterol or low-density lipoprotein (LDL)-cholesterol, HDL-cholesterol, and blood pressure[1] have identified a 40% to 84% increase in the 10-year risk of CHD among nondiabetic subjects with metabolic syndrome.[4,5] These predictions have been confirmed by a prospective evaluation of incident cardiovascular events[6,7] and by a large survey indicating that in the U.S. general population the metabolic syndrome is associated with an increased risk of mortality from CHD (hazard ratio = 1.29).[8]

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An emerging body of research indicates that metabolic syndrome is more prevalent (range, 29%–63%) in schizophrenia and other psychiatric patients treated with antipsychotic drugs than in the general populations of the countries where these studies were conducted.[9–13] A consensus exists that second-generation antipsychotic medications (SGAs) can induce weight gain, insulin resistance, and dyslipidemia and that, together with genetic and lifestyle factors, these drug-related abnormalities contribute to the high rate of metabolic syndrome in this population.[14–17] While there is still great controversy about the relative contribution of individual antipsychotic drugs to the metabolic abnormalities observed in SGA-treated populations, recent data suggest that clozapine and olanzapine are associated with a higher risk than risperidone and quetiapine, which, in turn, appear to have a higher risk compared to ziprasidone and aripiprazole.[18] Clinical guidelines have suggested that these metabolic abnormalities may lead to a greater vulnerability to CHD[18,19] and thus may contribute to the well-described excess of cardiovascular deaths among patients with schizophrenia.[20–22] However, the extent to which the metabolic syndrome increases the risk of CHD events in patients treated with SGAs is not known.

In this study, we aimed to assess the prevalence of metabolic syndrome and its cross-sectional relation with the 10-year risk of CHD (angina pectoris, myocardial infarction, and sudden cardiac death) in patients with a variety of psychiatric disorders treated with second-generation antipsychotic drugs. In addition, we sought to examine predictors of increased CHD risk that were independent of the criteria on which the CHD risk calculation was based. We hypothesized that antipsychotic-treated patients with the metabolic syndrome have a substantially increased risk of CHD events compared to patients without the metabolic syndrome. Our expectation was that components of the metabolic syndrome that do not overlap with the Framingham model (i.e., central obesity, fasting hyperglycemia, and hypertriglyceridemia) would contribute to the risk of CHD events.

METHOD

General Procedures

In May 2004, the Pharmacy and Therapeutics Committee of the Zucker Hillside Hospital, a 230-bed, psychiatric tertiary care hospital of North Shore-Long Island Jewish Health System, instructed all physicians to follow the recommendations of the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes for the detection of metabolic complications in patients treated with SGAs.[18] The policy required that the following measures be obtained within 24 hours of admission, or as soon as clinically feasible: personal and family history of obesity, diabetes, dyslipidemia, hypertension, or cardiovascular disease; weight and height; waist circumference at the level of umbilicus; fasting plasma glucose; and fasting lipid profile. A schedule for the reassessment of weight and metabolic data was specified. The Committee also decided to monitor the compliance with these guidelines and the frequency of metabolic complications over a period of 12 months.

For the purpose of this chart review study, demographic information and clinical data, collected from the inpatient charts as part of the performance improvement initiative, were abstracted. The Institutional Review Board of the North Shore-Long Island Jewish Health System approved the study.

Patient Population

Admission clinical and biochemical data were collected from the medical records of 460 psychiatric inpatients treated with SGAs at the time of presentation to the hospital's intake unit. Patient charts were randomly selected from consecutive admissions between August 1, 2004, and March 1, 2005. Ninety-three subjects were excluded from this study, leading to a total sample of 367 patients with complete data. Reasons for exclusion included (1) age younger than 20 years or older than 79 years (N = 49), as these are outside the age range that was used in the Framingham model of the 10-year CHD risk,[1] and (2) missing values of variables in the clinical record required to make the diagnosis of metabolic syndrome or to calculate the 10-year CHD risk (N = 44).

Definition of the Metabolic Syndrome

As defined by NCEP,[1] the metabolic syndrome was diagnosed in patients who fulfilled 3 or more of the following 5 criteria: waist circumference at the level of umbilicus greater than 88 cm in women and greater than 102 cm in men, fasting blood glucose level of 110 mg/dL or greater, serum triglyceride level of 150 mg/dL or greater, HDL-cholesterol level less than 40 mg/dL in men and less than 50 mg/dL in women, and arterial blood pressure 130/85 mm Hg or greater. Current treatment with antihypertensive medications fulfilled the metabolic syndrome criterion for high blood pressure. Treatment with lipid-lowering drugs fulfilled the metabolic syndrome criteria for low HDL-cholesterol and high triglycerides. A diagnosis of diabetes mellitus fulfilled the fasting hyperglycemia criterion. In addition, we used a fasting glucose level of 100 mg/dL or greater to assess the frequency of metabolic syndrome according to changes suggested by the International Diabetes Federation (IDF).[23]

Fasting blood glucose levels were measured at bedside with Accu-Chek Inform, Model 2001201; Roche; Mannheim, Germany. This microreflectometric method has excellent overall correlation (r = 0.974) with the standard laboratory glucose-oxidase method for serum

glucose levels up to 400 mg/dL.[24] The fasting lipid levels were measured spectrophotometrically at the Long Island Jewish Medical Center laboratory with the Chemistry Immunanalyzer, Model AU 2700; Olympus; Melville, N.Y.

Calculation of the 10-Year Risk of Coronary Heart Disease Events

The 10-year risk of CHD events, expressed as a percentage, for nondiabetic patients was calculated with the NCEP version of the Framingham score, a gender-specific instrument that assigns points for age, total cholesterol, HDL-cholesterol, blood pressure, and cigarette smoking, whereby the score for blood pressure is adjusted upward if a patient receives antihypertensive treatment.[1] For example, a 50-year-old man who smokes and has a total cholesterol level of 220 mg/dL, an HDL-cholesterol level of 38 mg/dL, and an untreated systolic blood pressure of 135 mm Hg will accumulate 15 points, corresponding to a 10-year risk of CHD events of 20%. A woman with identical parameters will have a 10-year risk of CHD events of 6%. The 10-year risk of CHD in diabetic patients was assessed with a version of the Framingham algorithm that assigns points for the presence of diabetes.[25]

Data Analyses

The 10-year CHD risk rates for male and female patients with and without the metabolic syndrome were corrected for age and race, and relative risk ratios were calculated by dividing the 10-year risk of CHD events in patients with metabolic syndrome by the rates found in patients without the metabolic syndrome. Analyses of variance and χ^2 tests were used to compare demographic and treatment variables, as well as the 10-year CHD risk by age group and gender in patients with and without the metabolic syndrome. Using the Bonferroni formula for multiple comparisons, the significance level was set at $p < .005$ (i.e., 0.05/10) for each of the 2-tailed, univariate analyses of the association between sex or race and metabolic syndrome criteria, at $p < .0021$ (i.e., 0.05/24) for the 2-tailed, univariate analyses of the association between metabolic syndrome and demographic or treatment variables, and at $p < .0036$ (i.e., 0.05/14) for the 2-tailed, univariate analyses of the association between 10-year risk of CHD events and demographic or treatment variables. Backward elimination, multiple logistic regression analysis was used to determine the significant contribution of nonpharmacologic variables that were not part of the Framingham model to the 10-year risk of CHD, i.e., primary psychiatric diagnosis, race, body mass index (BMI), waist circumference, fasting triglyceride levels, fasting glucose levels, and history of CHD events. Only those variables that reached a $p < .05$ in univariate analyses were entered in the multiple regression analyses. Data were analyzed using JMP 5.0.1, 1989–2003, SAS Institute Inc., Cary, N.C.

RESULTS

Sample Characteristics

Of the total sample of 367 patients with a mean ± SD age of 42.9 ± 15.3 years, 198 (54.0%) were male and 244 (67.6%) were white. The mean BMI was 28.6 kg/m^2, 51 patients (13.9%) were diabetic, and 201 (54.8%) smoked cigarettes daily (Table 1). The most frequent primary psychiatric diagnosis was schizophrenia or schizoaffective disorder (48.0%), followed by bipolar disorder (20.7%) and a depressive disorder (20.7%), while substance use disorders (4.6%), dementia (2.4%), and other psychiatric diagnoses (3.5%) were less common. The most frequently prescribed SGA in this population was olanzapine (N = 118, 32.1%), followed by quetiapine (N = 108, 29.4%), risperidone (N = 103, 28.1%), aripiprazole (N = 36, 9.8%), ziprasidone (N = 30, 8.2%), and clozapine (N = 28, 7.6%). In addition, 190 patients (51.8%) were treated concomitantly with anxiolytics or hypnotics, 169 (46.1%) with antidepressants, 134 (36.5%) with mood-stabilizing agents, and 66 (18.0%) with other nonantipsychotic psychotropic medications.

Metabolic Syndrome

One hundred thirty-seven (37.3%) of the 367 patients fulfilled the NCEP definition of the metabolic syndrome. By contrast, 174 patients (47.4%) fulfilled the definition of the metabolic syndrome when a glucose level of 100 mg/dL instead of 110 mg/dL was used for hyperglycemia, as proposed by the IDF. Current treatment with antihypertensive and/or lipid-lowering drugs contributed to the diagnosis of metabolic syndrome in 27 patients (20 treated only with lipid-lowering drugs, 4 treated only with antihypertensive medications, and 3 treated with both lipid-lowering and antihypertensive drugs). Regarding the association with demographic or treatment variables, patients with metabolic syndrome were older ($p < .0001$), had higher BMI values ($p < .0001$), and had higher frequencies of diabetes mellitus ($p < .0001$) and history of CHD ($p = .001$) (see Table 1).

Frequencies of the individual metabolic syndrome criteria are displayed in Table 2. Patients met a mean ± SD of 1.98 ± 1.38 of the 5 possible NCEP metabolic syndrome criteria. Low HDL-cholesterol (58.6%), high blood pressure (47.4%), and hypertriglyceridemia (41.4%) were the criteria most frequently met, while abdominal obesity (33.5%) and glucose levels ≥ 100 mg/dL (29.7%) or ≥ 110 mg/dL (17.2%) were less common. Female patients were significantly more likely to have abdominal obesity than the male patients included in this study ($p < .0001$). Hypertriglyceridemia was significantly more common among white compared to nonwhite patients ($p = .0041$).

Table 1. Demographic and Clinical Characteristics of Patients With and Without the Metabolic Syndrome[a]

Characteristic	Total Sample (N = 367)	Patients With Metabolic Syndrome (N = 137)	Patients Without Metabolic Syndrome (N = 230)	Statistic	p Value
Age, mean ± SD, y	42.9 ± 15.3	47.4 ± 15.3	40.2 ± 14.7	F = 20.33	< .0001
Male sex	198 (54.0)	75 (54.7)	123 (53.5)	χ^2 = 0.06	.81
White race[b]	244 (67.6)	94 (69.6)	150 (66.4)	χ^2 = 0.41	.52
Body mass index (kg/m^2), mean ± SD	28.6 ± 6.8	32.8 ± 7.3	26.4 ± 5.5	F = 88.78	< .0001
Smoking	201 (54.8)	85 (62.0)	116 (50.4)	χ^2 = 4.70	.030
History/presence of diabetes	51 (13.9)	41 (29.9)	10 (4.4)	χ^2 = 46.95	< .0001
History of CHD	29 (7.9)	19 (13.9)	10 (4.4)	χ^2 = 10.69	.0011
Primary psychiatric diagnosis					
Schizophrenia/schizoaffective disorder	176 (48.0)	74 (54.0)	102 (44.3)	χ^2 = 3.22	.073
Bipolar disorder	76 (20.7)	33 (24.1)	43 (18.7)	χ^2 = 1.50	.221
Depressive disorder	76 (20.7)	22 (16.1)	54 (23.5)	χ^2 = 2.96	.085
Substance use disorder	17 (4.6)	3 (2.2)	14 (6.1)	χ^2 = 3.29	.070
Dementia	9 (2.4)	3 (2.2)	6 (2.6)	χ^2 = 0.06	.800
Other	13 (3.5)	2 (1.5)	11 (4.8)	χ^2 = 3.16	.076
Second-generation antipsychotics[c]					
Olanzapine	118 (32.1)	45 (32.8)	73 (31.7)	χ^2 = 0.05	.826
Quetiapine	108 (29.4)	47 (34.3)	61 (26.5)	χ^2 = 2.48	.115
Risperidone	103 (28.1)	32 (23.4)	71 (30.9)	χ^2 = 2.44	.181
Aripiprazole	36 (9.8)	11 (8.0)	25 (10.9)	χ^2 = 0.80	.370
Ziprasidone	30 (8.2)	12 (8.8)	18 (7.8)	χ^2 = 0.10	.753
Clozapine	28 (7.6)	15 (11.0)	13 (5.7)	χ^2 = 3.30	.069
Nonantipsychotic treatment [c]					
Anxiolytics/hypnotics	190 (51.8)	67 (48.9)	123 (53.5)	χ^2 = 0.72	.397
Antidepressants	169 (46.1)	61 (44.5)	108 (47.0)	χ^2 = 0.20	.651
Mood stabilizers	134 (36.5)	56 (40.9)	78 (33.9)	χ^2 = 1.79	.181
Other psychotropic drugs	66 (18.0)	29 (21.2)	37 (16.1)	χ^2 = 1.48	.224

[a]Data shown as N (%) unless otherwise noted.
[b]Six patients without ethnic information.
[c]Total N > 367 due to polypharmacy.
Abbreviation: CHD = coronary heart disease.

Ten-Year Risk of Coronary Heart Disease Events

The overall calculated age- and race-corrected 10-year risk of CHD was 8.29% (SE = 0.49) in men and 2.33% (SE = 0.52) in women (risk ratio = 3.56, 95% CI = 3.20 to 3.92, p < .0001) (Figure 1). The risk was significantly greater in men compared to women in all age groups. The overall calculated age-, sex-, and race-corrected 10-year risk of CHD was 6.71% (SE = 0.49) in smokers and 3.80% (SE = 0.51) in nonsmokers (risk ratio = 1.76, 95% CI = 1.58 to 1.94, p < .0001) (Figure 2). The risk was significantly greater in smokers compared to nonsmokers in the 2 age groups below 60 years.

Compared with the rest of the cohort, patients with metabolic syndrome had a significantly higher age-, sex-, and race-corrected 10-year risk of CHD events, i.e., 7.99% (SE = 0.56) vs. 3.70% (SE = 0.44) (risk ratio = 2.16, 95% CI = 1.94 to 2.38, p < .0001). The gender-specific risk ratios comparing the CHD risk in patients with and without metabolic syndrome were 2.18 (95% CI = 1.88 to 2.48, p < .0001) for men (i.e., 11.45% [SE = 0.86] vs. 5.26% [SE = 0.69]) and 1.94 (95% CI = 1.65 to 2.23, p = .0005) for women (i.e., 4.46% [SE = 0.49] vs. 2.30% [SE = 0.38]) (Figure 3). The significantly increased risk of CHD in patients with metabolic syndrome was identified in 5 of the 6 age and gender subgroups.

Subgroup analyses of the sex-, age-, and race-adjusted 10-year CHD risk in patients with or without diabetes mellitus yielded similar results, with patients having both diabetes and metabolic syndrome scoring the highest. The adjusted 10-year risk of CHD events of diabetic patients with (N = 41) and without (N = 10) the metabolic syndrome was 14.19% (SE = 1.60) vs. 1.98% (SE = 3.24) (risk ratio = 7.17, 95% CI = 5.20 to 9.14, p = .0011). The risk of CHD of nondiabetic patients with (N = 96) and without (N = 220) metabolic syndrome was 5.65% (SE = 0.49) vs. 3.45% (SE = 0.33) (risk ratio = 1.64, 95% CI = 1.46 to 1.82, p = .0001).

In multivariate analyses of demographic and metabolic variables that are not part of the Framingham model, fasting triglyceride levels (p < .0001), waist circumference (p = .035), and white race (p = .047) were significantly associated with the 10-year risk of CHD in the nondiabetic subsample (R^2 = 0.134; p < .0001). Nondiabetic patients with (N = 36) and without (N = 278) these 3 characteristics had a 10-year risk of CHD of 11.31% (SE = 2.06) vs. 5.57% (SE = 0.58) for men (risk ratio = 2.03, 95% CI = 1.72 to 2.34, p = .0068) and 4.65% (SE = 1.29) vs. 1.84% (SE = 0.30) for women (risk ratio = 2.53, 95% CI = 2.12 to 2.94, p = .0019).

DISCUSSION

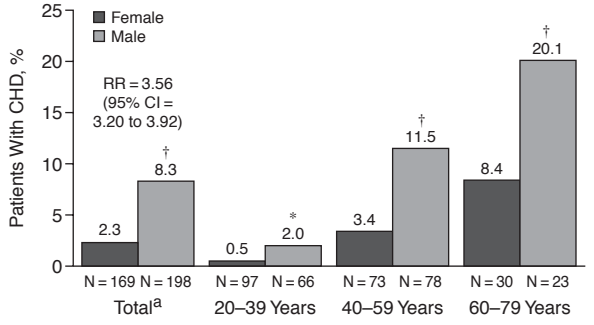
This cross-sectional study of 367 adults treated with SGAs found that the metabolic syndrome was present in

Table 2. Frequency of Metabolic Syndrome Criteria in Patients Treated With Second-Generation Antipsychotics

Characteristic	All (N = 367)	Men (N = 198)	Women (N = 169)	White (N = 244)	Nonwhite (N = 117)
NCEP criteria					
Metabolic syndrome, N (%)	137 (37.3)	75 (37.9)	62 (36.7)	94 (38.5)	41 (35.0)
No. of criteria met, mean ± SD	1.98 ± 1.38	1.97 ± 1.34	1.98 ± 1.44	2.02 ± 1.39	1.87 ± 1.37
IDF criteria					
Metabolic syndrome, N (%)	174 (47.4)	98 (49.5)	76 (45.0)	119 (48.8)	52 (44.4)
No. of criteria met, mean ± SD	2.10 ± 1.41	2.11 ± 1.36	2.09 ± 1.48	2.15 ± 1.42	1.97 ± 1.41
Criteria met, N (%)[a]					
Waist	123 (33.5)	45 (22.7)	78 (46.2)[b]	81 (33.2)	39 (33.3)
Blood pressure	174 (47.4)	106 (53.5)	68 (40.2)	112 (45.9)	58 (49.6)
Triglycerides	152 (41.4)	92 (46.5)	60 (35.5)	113 (46.3)[c]	36 (30.8)
HDL-cholesterol	215 (58.6)	111 (56.1)	104 (61.5)	146 (59.8)	65 (55.6)
Glucose (NCEP)	63 (17.2)	36 (18.2)	27 (16.0)	41 (16.8)	22 (18.8)
Glucose (IDF)	109 (29.7)	64 (32.3)	45 (26.6)	74 (30.3)	34 (29.3)

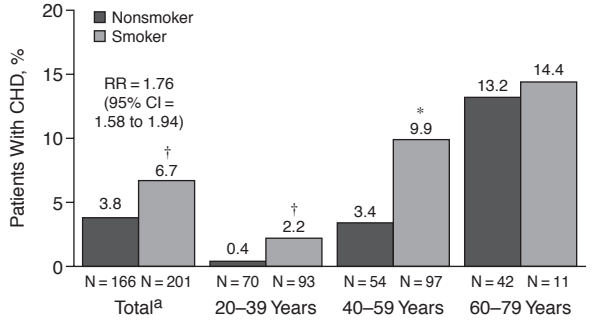
[a]Criteria are as follows: waist > 88 cm in women and > 102 cm in men, blood pressure 130/85 mm Hg or greater, triglycerides ≥ 150 mg/dL, HDL-cholesterol < 40 mg/dL in men and < 50 mg/dL in women, and glucose ≥ 110 mg/dL (NCEP) or ≥ 100 mg/dL (IDF).
[b]Gender difference for waist circumference: $\chi^2 = 22.6$, df = 1,366; p < .0001.
[c]Race difference for hypertriglyceridemia: $\chi^2 = 8.22$, df = 1,359; p = .0041.
Abbreviations: HDL = high-density lipoprotein, IDF = International Diabetes Federation, NCEP = National Cholesterol Education Program.

Figure 1. Ten-Year Coronary Heart Disease (CHD) Risk in Patients Treated With Second-Generation Antipsychotics: Effect of Sex by Age Group



[a]Adjusted for age and race.
*p < .0008.
†p < .0001.
Abbreviations: CI = confidence interval, RR = risk ratio.

Figure 2. Ten-Year Coronary Heart Disease (CHD) Risk in Patients Treated With Second-Generation Antipsychotics: Effect of Smoking Status by Age Group



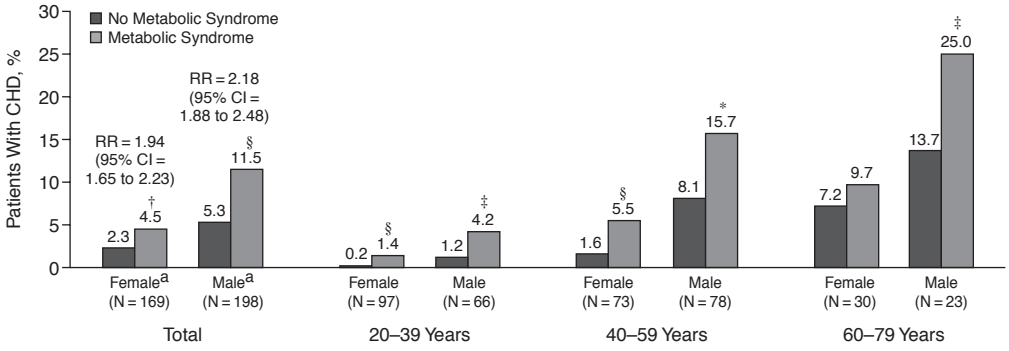
[a]Adjusted for sex, age, and race.
*p < .0002.
†p < .0001.
Abbreviations: CI = confidence interval, RR = risk ratio.

more than one third of the study cohort with mixed psychiatric disorders. The presence of the metabolic syndrome doubled the 10-year risk of CHD predicted by the Framingham point score in both men and women. The excess risk remained significant in the subgroup of nondiabetic patients, and more than tripled when the analyses were repeated in diabetic patients. Among the variables that were independent of the Framingham point scoring system, the 10-year risk of CHD events was significantly associated with fasting hypertriglyceridemia, abdominal obesity, and white race.

The rate of metabolic syndrome in our population (37.3% for the entire sample, 37.9% in men and 36.7% in women) was substantially higher than the age-adjusted U.S. population-based rate of 23.7%.[3] The finding is consistent with previous studies of schizophrenia patients treated with SGAs.[9–12] However, the rates found in these studies are variable and depend on the characteristics of the study population, including distribution of age, gender, and proportion of minority subjects.

Because we have also calculated the prevalence of the metabolic syndrome using a fasting glucose threshold of 100 mg/dL (47.4% for the entire sample, 45% for men, and 48.8% for women), our findings are best compared with those generated by an analysis of 689 subjects from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) in which the prevalences of metabolic syndrome calculated with the standard NCEP rule and the modified glucose level were 36% and 36.6% for males and 51.6% and 54.2% for females.[13] The basic dif-

Figure 3. Ten-Year Coronary Heart Disease (CHD) Risk in Patients Treated With Second-Generation Antipsychotics: Effect of Metabolic Syndrome by Sex and Age Group



[a]Adjusted for age and race.
*p < .005.
†p = .0005.
‡p < .0005.
§p < .0001.
Abbreviations: CI = confidence interval, RR = risk ratio.

ference between our cohort and the CATIE sample is the higher prevalence of metabolic syndrome among females enrolled in CATIE. The explanation is most likely due to the fact that compared with our sample, females enrolled in CATIE had a much higher prevalence of abdominal obesity (73.4% vs. 46.2%; difference of 27.2%). The absolute difference for males was only 10.9% (33.6% vs. 22.7%). The 2 populations were similar with regard to the prevalence of the blood pressure, lipids, and fasting glucose criteria, as well as the 2:1 female:male ratio among patients meeting the criterion for abdominal obesity. Differences in primary psychiatric diagnosis groups may have also played a role, since only 46.1% of our sample had schizophrenia. The higher prevalence of abdominal obesity in males and females in CATIE suggests that schizophrenia itself may be associated with increased abdominal fat.[26] However, it is important to remember that all of these studies have a cross-sectional design, individual findings must be interpreted cautiously, and prospective studies are required to determine the contribution of SGAs relative to other risk factors, such as psychiatric illness, genetic vulnerability, sedentary lifestyle, and atherogenic diet.

In the 2 U.S.-based community surveys of nondiabetic patients available to date, the presence of metabolic syndrome was associated with age-, gender-, and race-corrected CHD risk ratios of 1.4[4] and 1.84.[5] The risk ratio of 1.64 in our 316 nondiabetic patients fits in the middle of this reference range. On the other hand, the doubling in CHD risk associated with metabolic syndrome estimated for our entire antipsychotic-treated patient cohort appears to be higher than expected for a population in which only 13.9% of subjects had diabetes mellitus, as the CHD risk was similar to that reported in a large Scandinavian community sample in which 38% of the subjects had type 2 diabetes.[27] The high risk of CHD in our diabetic subsample compared to the nondiabetic group is particularly worrisome in view of the diabetogenic risk of some of the SGAs, in particular clozapine and olanzapine.[16–19]

The age- and race-adjusted overall 10-year risk for CHD identified in our study (8.3% in men and 2.3% in women) is fairly consistent with the findings from the only other 2 studies that have calculated 10-year CHD risk estimates in antipsychotic-treated patients.[10,28] In a Canadian study of 240 schizophrenic patients,[10] antipsychotic-treated males had a significantly higher 10-year CHD risk compared to a national reference group (8.9% vs. 6.3%), but the difference was not significant in females (2.6% vs. 2.0%). In a U.S. sample,[28] the 10-year CHD risk was assessed in 689 schizophrenia patients enrolled in the CATIE and compared with that of age-, gender-, and race-matched control subjects from the Third National Health and Nutrition Examination Survey (NHANES III). In this study, the risk was significantly elevated in both men (9.4% vs. 7.4%) and women (6.3% vs. 4.2%). These rates seem to be a fairly accurate prediction, given a 10-year Kaplan-Meier estimate of 9% in the only study that prospectively observed cardiovascular mortality in patients with schizophrenia or schizoaffective disorder who received clozapine treatment.[22] Of note, in this sample, the Kaplan-Meier estimate for emerging diabetes during the 10-year follow-up period was 43%, which may further increase the CHD mortality rates after the onset of diabetes.

Despite the high prevalence rates of metabolic syndrome observed in populations receiving antipsychotic medications,[9–12] to date, none of the studies evaluating[22] or calculating[10,28] the 10-year CHD risk rates have as-

sessed the impact of metabolic syndrome on the CHD risk estimates. While the finding of an elevated risk in patients with the metabolic syndrome (11.5% in men and 4.5% in women) is consistent with the literature in nonpsychiatric samples,[4–8] the 2-fold increase in the predicted 10-year CHD risk in our study population with NCEP-defined metabolic syndrome is approximately 30% higher than the risk ratio of 1.65 (95% CI = 1.38 to 1.99) for cardiovascular disease observed in prospective studies in the general population.[29] This highlights the need to prospectively assess the actual risk of incident cardiovascular disease in psychiatric patients treated with SGAs. The true rates may be different, as factors not included in the Framingham point score system could play an important role in mediating the risk for cardiovascular illness in patients suffering from major psychiatric disorders who are exposed to antipsychotic medications.

In the present study, the unique contribution of the metabolic syndrome to the CHD risk suggested by the NCEP[1] and others[6–8] was confirmed by the strong correlation between the predicted risk and triglyceride levels as well as waist circumference. High triglyceride levels have been identified in young adults who die suddenly and unexpectedly from clinically silent CHD,[30] in middle-aged men without preexisting ischemic heart disease,[31] and in elderly women with myocardial infarction, ventricular fibrillation, and sudden cardiac death.[32] Triglyceride levels correlated strongly with the risk of CHD in our study, a finding that confirms the NCEP view that elevated hypertriglyceridemia contributes to the risk of CHD and may be produced or worsened by excess weight and cigarette smoking,[1] both of which are prominent features of our patient population.

Our findings also support studies that have identified central obesity as a predictor for CHD after adjusting for total adiposity.[33,34] However, we must point out that this correlation is still subject to some debate, fueled by the results of the National Health and Nutrition Examination Survey II, in which excess weight was not independently associated with mortality from CHD[8]; the findings of the Honolulu Heart Program, in which the relationship of waist circumference with CHD was found to be mediated through a relation with the HDL-cholesterol level[35]; and the data generated by the Physicians' Health Study, which demonstrated that abdominal obesity was associated only with a very modest increase in the risk of CHD in middle-aged and older men.[36] Nonetheless, central obesity is a major cause of the insulin resistance and hypertriglyceridemia observed in psychiatric patients,[15,16] and the "hypertriglyceridemic waist" identified by our regression analysis in this group of patients is known to be associated with fasting hyperinsulinemia, hyperapolipoprotein B, and increased concentration of small, dense LDL-cholesterol particles.[37] Results from this study confirm our previous finding from an independent cohort showing a strong association between abdominal obesity and metabolic syndrome in SGA-treated adults with mixed psychiatric diagnoses.[11] In addition, these results are also consistent with angiographically proven observations of a significantly increased CHD risk in nondiabetic men with the hypertriglyceridemic waist.[37,38]

In our cohort, white and not minority race was associated with a significant increase in 10-year CHD risk. This finding may appear surprising, but it is consistent with studies that have found rates of metabolic syndrome to be higher in people with white race than in African American or other minority groups, being surpassed only by the rates in the Hispanic subgroup.[3,12] The race differential in diabetogenic and atherogenic risk factors has been demonstrated in work showing that African American obese adolescents have less visceral adiposity and lower insulin production than their white counterparts of similar BMI.[39] Race was also the strongest demographic predictor for blood lipids, with greater HDL-cholesterol levels and lower total cholesterol/HDL-cholesterol ratios in obese African American patients.[40] However, a recent analysis of the 1988–1994 National Health and Nutrition Examination Survey (NHANES III) has shown minimal race or ethnic variation when the data were stratified by gender,[41] and we agree with the opinion that the interaction between metabolic risk of SGAs and race/ethnicity is complex and requires further study.[42]

In evaluating the results of this study, certain limitations need to be considered. These include the cross-sectional design, lack of information about the past duration and type of antipsychotic treatment exposure, lack of reliable data about the minority racial and ethnic distributions, and lack of a matched control group. Furthermore, to err on the side of a conservative CHD risk estimation and to match clinical practice settings, we chose not to exclude patients from the analyses who were treated with lipid-lowering agents, which could have lowered the CHD risk calculation artificially, as in the Framingham point scoring system a risk adjustment is only made for current antihypertensive treatment. Finally, the Framingham algorithm for the prediction of CHD risk was developed and validated in population samples not exposed to SGAs. Therefore, we cannot exclude the possibility that the treatment with SGAs and the underlying psychiatric disorders could modify the risk of CHD through mechanisms that are independent of traditional risk factors for coronary atherosclerosis. Nonetheless, this work is a robust confirmation of the high prevalence of metabolic syndrome in patients with a variety of psychiatric disorders treated with SGAs and the first attempt to evaluate the association between presence of the metabolic syndrome and the risk of coronary heart events in psychiatric patients.

The NCEP position is that the metabolic syndrome is part of a constellation of unhealthy life habits, major risk factors, and "candidate" risk factors. NCEP argues further

that, at the present time, the syndrome should be seen as the secondary target of risk reduction therapy, the primary target being the reduction of LDL-cholesterol level.[1] These assumptions have been challenged recently in a joint statement from the American Diabetes Association and the European Association for the Study of Diabetes,[43] which argued that the syndrome has been imprecisely defined, that its 5 components should not be weighed equally, and that its value as a risk marker for CHD is doubtful or very limited. This stance has been debated in a statement of the American Heart Association/National Heart, Lung, and Blood Institute whose authors concluded that the NCEP 5-component cluster is truly a syndrome and that it identifies individuals at an elevated risk of CHD.[44]

In patients treated with SGAs, the metabolic syndrome appears to have a strong contribution to the risk of CHD. Our data indicate that this correlation is not a tautology due to the overlap between the metabolic syndrome criteria and the traditional risk factors used to calculate the risk of CHD according to the Framingham system. We believe that the metabolic syndrome adds a relatively specific contribution to the risk identification in patients through the nontraditional risk factors of hypertriglyceridemia and abdominal obesity. It is conceivable that additional risk markers that are more proximal to the CHD outcome, such as prothrombotic and inflammatory markers,[45,46] may further enhance the predictive power of a new to-be-defined metabolic syndrome. However, until such evidence becomes available, clinicians should monitor patients for each of the individual risk criteria of the metabolic syndrome, as well as for the risk constellation, and target each abnormality.[43]

In view of the 2-fold increase in the predicted 10-year CHD risk in SGA-treated patients with the metabolic syndrome, clinicians need to consider metabolic risks of treatments and unhealthy lifestyle behaviors, together with the identification and treatment of patients with elevated LDL-cholesterol, as the primary targets for CHD prevention.[1] The LDL-cholesterol level must be lowered to less than 100 mg/dL in patients with diabetes, CHD equivalents (i.e., abdominal aortic aneurysm, peripheral arterial disease, and symptomatic carotid artery disease), and estimated 10-year CHD risk of greater than 20%. An LDL-cholesterol level less than 130 mg/dL is the target for patients with risk factors common among psychiatric patients in general and those with metabolic syndrome in particular (e.g., smoking, HDL-cholesterol less than 40 mg/dL, hypertension) who have a 10% to 20% 10-year risk of CHD.[1] It has been argued that having a diagnosis of schizophrenia or bipolar disorder alone is sufficient to require LDL-cholesterol levels of less than 130 mg/dL.[19] Major efforts must be made in all psychiatric settings to initiate and aggressively pursue these goals, to promote smoking cessation, and to obtain weight reduction and optimal control of hypertension, diabetes, and hypertriglyceridemia.[19] Men 40 years and older, patients with a history of CHD, and patients with the "hypertriglyceridemic waist" are at higher risk and need sustained attention. The clinical benefits of second-generation antipsychotics are a precious advantage in the struggle to improve the quality of life of psychiatric patients, but this advantage can be maintained only through the recognition and efficient management of their metabolic complications and the increased risk of coronary heart disease.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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