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Obesity and Coronary Risk in Patients Treated With Second-Generation Antipsychotics

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Abstract

Background—Weight gain leading to obesity is a frequent adverse effect of treatment with atypical antipsychotics. However, the degree of its independent contribution to the risk of coronary heart disease events in patients treated with these drugs has not been elucidated.

Objective—To determine whether obesity is an independent risk factor for the 10-year risk of coronary heart disease events in psychiatric patients treated with atypical antipsychotics.

Method—We used the Framingham method, which is based on age, gender, blood pressure, smoking, and plasma levels of total and high-density lipoprotein cholesterol, to estimate the 10-year risk of coronary heart disease events in patients treated with second-generation antipsychotics who were obese (N=44; mean age 38.1 years, 54.5% males) or normal weight (N=83; mean age 39.9 years, 47.0% males). Excluded were patients with metabolic syndrome and those taking antihypertensive, hypoglycemic and lipid-lowering drugs.

Results—The 10-year risk of coronary artery disease events was very low and virtually identical in the obese and normal weight patients (2.3±3.5 vs. 2.6±4.6, p=.68) despite excess of 12 BMI units (p<0.0001) and 15.7 cm waist circumference (p<0.0001) in the obese. The risk was similar in obese and normal weight males (3.8±5.9 vs. 2.8±3.4, p=0.45) and females (1.7±3.7 vs. 1.5±2.5, p=0.83).

Limitations—The validity of the 10-year prediction for risk of coronary heart disease events in the mentally ill based on the Framingham score system requires prospective confirmation.

Conclusions—Obesity does not appear to be an independent predictor for the 10-year risk of coronary heart disease events in patients without metabolic syndrome treated with second-generation antipsychotics.

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Keywords

Antipsychotics; Obesity; Normal Weight; Metabolic Syndrome; Coronary Heart Disease Events; Risk

Obesity (body mass index (BMI) >30 kg/m^2) is highly prevalent among patients with schizophrenia (2) and bipolar disorder (21) and is more common in persons with these conditions than in the general US population (27). Excess weight is a major risk factor for impaired glucose tolerance, atherogenic dyslipidemia and arterial hypertension, and the clustering of obesity with these abnormalities in the metabolic syndrome correlates strongly with increased risk of coronary heart disease and premature death in all ethnic groups and regions of the world (6, 16, 23,26). Treatment with atypical, second-generation antipsychotics (SGAs), particularly clozapine, olanzapine and quetiapine, are known to promote weight gain, may lead to metabolic syndrome, an association of intraabdominal fat accumulation with impaired insulin sensitivity, hypertension and changes in lipid profile that increases the risk of coronary heart disease (8,11,16,26). The estimated 10-year risk of coronary events is at least double in patients receiving antipsychotics who have metabolic syndrome studied in USA (8) and Europe (6).

A substantial proportion of obese individuals in the general population do not have the abnormalities that define the metabolic syndrome (7,17,20,29). These individuals are referred to as “metabolically healthy obese” and longitudinal studies with up to 13 years of follow up have suggested that their cardiovascular morbidity is similar to that of normal weight persons (22,28). These findings expand on the data collected three decades ago on the predictors of the 618 deaths from coronary heart disease in a seven-country cohort of 11,579 men followed for 15 years, in which age, serum cholesterol, blood pressure and smoking were highly significant predictors of cardiac death in all regions, but weight was not a significant predictor anywhere (18). In another study of 16,113 persons followed for 15 years, the findings have been interpreted to suggest that obesity is an independent risk factor for coronary heart disease mortality, but data indicate that after adjustment for smoking, serum cholesterol and blood pressure the BMI-associated risk ratio of coronary heart disease mortality was only 1.03 (19). However, similar studies have not been performed in populations of patients with psychiatric disorders who may have been put at increased risk for coronary heart disease events by the psychotropic-induced weight gain.

Our group has recently reported that the weight gain that follows the administration of atypical antipsychotics is not always associated with unfavorable changes in lipid concentrations, decreased insulin sensitivity or emergence of metabolic syndrome, at least short-term in young patients (9). The preservation of metabolic heath in obese adults treated with drugs from the same class has not yet been the subject of a focused study. In the work presented here, we attempted to determine whether obesity is an independent risk factor for coronary heart disease in psychiatric patients treated with SGAs. We used data generated by a study of 364 patients receiving SGAs who were consecutively admitted to a single, acute-care psychiatric hospital (8) to identify obese and normal weight patients who could be considered metabolically healthy and hypothesized that the two groups will demonstrate similarly low 10-year risk of clinical events produced by coronary heart disease, despite treatment with antipsychotics and presence of a psychiatric illness warranting such treatment.

Methods

Selection of Subjects

Demographic and clinical data were collected from records of 458 patients randomly selected from 1,420 consecutive admissions to a single 230-bed psychiatric hospital from 8.1.2004 – 3.1.2005. Psychiatric diagnoses were made by board certified psychiatrists. Smoking was coded as present when daily use was reported. The Institutional Review Board of the hospital approved the study. Fasting blood glucose and lipid levels were measured microreflectometrically and spectrophotometrically, respectively, as described before (8). Metabolic syndrome was defined by ≥3/5 criteria: waist circumference at the level of umbilicus >88 cm in women and >102 cm in men; fasting blood glucose ≥110 mg/dL; serum triglycerides ≥150 mg/dL; HDL-cholesterol <40 mg/dL in men and <50 mg/dl in women; and arterial blood pressure ≥130/85 (15). We excluded patients <20 years and >79 years old (N=49), and patients without data required to calculate BMI (N=45) yielding a cohort of 364 patients (8). The study sample consisted of psychiatric inpatients who underwent fasting blood draws on the morning after admission according to the hospital policy.

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

Data were extracted for the 44 obese patients (BMI greater than 30) and the 87 patients with normal weight (BMI: 18.5–24.9) who had no evidence of metabolic syndrome (15) and who were not currently receiving treatment with antihypertensive, hypoglycemic or lipid-lowering drugs. The 10-year risk of coronary heart disease events (angina pectoris, myocardial infarction and sudden death), expressed as a percentage, was estimated with the National Cholesterol Education Program version of the Framingham score, which uses data regarding age, gender, smoking status, blood pressure, total cholesterol and high-density lipoprotyein cholesterol (13). The method has been extensively validated (12) and has been strongly recommended for use in clinical settings by the American Heart Association (15).

Statistical Analyses

Analyses of variance and chi-square tests were used to compare variables in obese and normal weight patients. The Bonferroni correction was applied to clusters of dependent variables. A stepwise backward elimination multiple regression analyses was conducted comparing normal weight and obese patients entering all variables into the initial model that reached $p<0.1$ in univariate comparisons, except for waist circumference and BMI. Analyses were two-sided, with alpha of $p<0.05$, using JMP 5.0.1, 1989–2003, SAS Institute Inc.

Results

Demographic and Clinical Characteristics

Compared to normal weight patients, obese patients without the metabolic syndrome were less likely to be White ($p=0.011$), smokers ($p=0.030$), and treated with quetiapine ($p=0.024$), more likely to have a primary substance use disorder diagnosis ($p=0.0035$) and to be treated with first generation antipsychotics ($p=0.030$), and, by design, had significantly greater BMI ($p<0.0001$). After Bonferroni correction for clusters of variables, normal weight and obese patients did not differ significantly regarding demographic, diagnostic and pharmacological characteristics, except for the expected greater BMI in the obese (Table 1).

Anthropometric and Metabolic Features

The obese patients had a 15.7 cm larger waist circumference than the normal weight patients (97.0±16.8 vs. 81.3±6.6, $p<0.0001$). The proportion of patients with abdominal obesity,

defined by waist circumference greater than 40 inches (102 cm) in men and 35 inches (88 cm) in women, was significantly higher in the obese group (n=16, 36.4%) compared to the normal weight group (n=2, 2.4%, p<0.0001). The categorical and continuous values of all other metabolic syndrome components were not significantly different in the two groups (Table 2).

Except for diastolic blood pressure, which was 4.3 mm Hg higher in the obese (p=0.0078), and LDL-cholesterol, which was 8.9 mg/dL higher in the obese(p=0.046), differences remained non-significant after controlling for the five variables that in univariate analyses differed between the two groups at p<0.1(excluding BMI, see Table 1).

Logistic regression

A regression model (which excluded waist circumference and BMI that were different based on *a priori* grouping) explaining 14% of the variance (p<0.0001) showed that compared to normal weight patients, obese patients were less likely daily cigarette smokers (p=0.010) and more likely to have a primary substance use disorder (p=0.011), diastolic blood pressure >78 mm Hg (p=0.022) and first-generation antipsychotic co-treatment (p=0.036). The model components and statistics did not change whether substance abuse was entered as a primary (n=7) or primary/comorbid (n=25) diagnosis, or as individual substance abuse categories.

10-Year Risk of Coronary Events

Obese and normal weight patients had a low and essentially identical 10-year risk of coronary heart disease events (2.3± 3.5 vs. 2.6±4.6, p=0.68) (Table 2). The risk of coronary heart disease events was also similar in the subgroups of males (3.8±5.9 vs. 2.8±3.4, p=0.45) and females (1.7±3.7 vs. 1.5±2.5, p=0.83). Furthermore, the 10-year risk of coronary heart disease events was similar in the obese or normal weight patients with abdominal obesity (2.5± 3.6 vs. 2.6±4.6, p=0.87) and without abdominal obesity (1.9± 3.5 vs. 2.0±1.4, p=0.98).

Discussion

In this cross sectional study, obese and normal weight psychiatric patients without metabolic syndrome had a similar 10-year risk of coronary heart disease events, despite a very large difference in BMI (34.1 vs. 22.1). Although the findings are based on an estimate rather than direct observation, they are similar to data reported in carefully conducted follow up studies. In a community-based, longitudinal study of 2,902 people (55% women, mean age 53 years) which included 638 obese subjects, only the risk factor clustering or the presence of insulin resistance appeared to confer the risk for diabetes or cardiovascular disease commonly associated with elevated BMI (22). Likewise, in a 13-year longitudinal study of 1,824 nondiabetic patients, the obese men without features of the metabolic syndrome had a statistically similar risk of ischemic heart disease events as that observed in normal weight participants (28). Moreover, in a recent validation of the Framingham prediction score performed on 4,175 Australian men followed from 1989–2004, the BMI did not predict deaths for coronary heart disease (12). Nonetheless, the validity of these findings should be accepted only within a time frame that does not exceed 15 years, because a recent report has identified a correlation between obesity and cardiovascular morbidity and mortality after 30 years of follow-up, independent of metabolic syndrome status (5).

Our study has identified a small difference in the concentration of LDL-cholesterol between the obese and the normal weight groups and it is possible that this “dyslipidemic gap” will deepen and acquire pathologic significance decades later. Of interest is also that the prevalence of cigarette smoking was significantly lower in our obese patients as compared with the normal weight group. Smoking is an important contributor to the risk of future

coronary events and it is encouraging to note this favorable trend in some psychiatric patients. Smoking cessation may lead to weight gain, but it has a favorable effect on lipid metabolism and insulin sensitivity (14) and therefore may contribute to attaining metabolic health in the obese (20).

Our data are consistent with those observed in non-psychiatric samples and indicate that in the absence of metabolic syndrome obesity is not an independent contributor to the risk of coronary heart disease events on a short or medium-term basis. The findings must be interpreted within the limitations of a modest sample size, mixed psychiatric diagnoses, non-random drug assignment, unavailable information about body mass index prior to the initiation of treatment with SGA, diet and exercise, and lack of direct assessments of insulin sensitivity and fat distribution. We also note that we defined metabolic syndrome according to the American Heart Association (15) which is the accepted standard for clinical and epidemiological studies in the United States. In Europe, most research on patients with metabolic syndrome has used the definition proposed by the International Diabetes Federation (1), which requires shorter waist circumference threshold for the validation of central adiposity than the American Heart Association (94 vs 102 cm for males and 80 vs 88 cm for females). A replication of our investigation in larger samples of patients from a variety of geographical locations around the world would certainly provide valuable information.

Our findings do not imply that obesity in patients treated with SGA's is merely a cosmetic nuisance. Obesity has been associated with reduced quality of life (3) and medication non-adherence (30) in patients with schizophrenia. Moreover, the search for the clinical and laboratory features of atherogenic dyslipidemia and inflammation, prediabetes, and metabolic syndrome in this population must be diligent and persistent, and all known risk factors must be treated aggressively. The American Psychiatric Association and American Diabetes Association (4) and the European Psychiatric Association (10) have published guidelines for the monitoring of body mass index, abdominal girth, arterial blood pressure and fasting glucose and lipid levels in patients with severe mental illness treated with antipsychotics. Unfortunately, compliance with these recommendations has been poor, as shown by a survey of a cohort of 109,451 patients receiving second-generation antipsychotics from California, Missouri and Oregon, in which fasting glucose was measured in 27% and lipids in only 10% of the sample (24). The initial testing rates were 27% for glucose and Smoking cessation, caloric intake reduction, increased energy expenditure through aerobic activities, and pharmacological interventions for dyslipidemia, glucose intolerance and elevated blood pressure should be advocated and monitored in all patients receiving antipsychotics. Given the insufficient metabolic monitoring in SGA treated individuals, efforts should be directed toward the increase of appropriate cardiovascular risk monitoring in these vulnerable patients.

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Table 1

Demographic and Clinical Characteristics at Time of Psychiatric Admission in Normal Weight and Obese Patients Without Metabolic Syndrome

Characteristic	Total [a] (N=127)	Normal Weight (BMI=18.5–24.9) (N=83)	Obese (BMI ≥ 30) (N=44)	F / chi^2	P-value
Demographic Variables					
Age (years ± SD)	39.3±14.9	39.9±14.5	38.1±15.8	F: 0.44	0.51
Sex (Male, N, %)	63 (49.6)	39 (47.0)	24 (54.5)	χ^2: 0.66	0.42
Race (White, N, %) [b]	80 (64.0)	59 (71.9)	21 (48.8)	χ^2: 6.54	**0.011**
Coronary Heart Disease Risk Factors					
Smoking (N, %)	63 (49.6)	47 (56.6)	16 (36.4)	χ^2: 4.72	**0.030**
History/Presence of diabetes (N, %)	2 (1.6%)	2 (2.4)	0 (0.0)	χ^2: 1.08	0.30
History of CAD (N, %)	3 (2.5)	2 (2.4)	1 (2.3)	χ^2: 0.002	0.96
Body mass index (kg/m^2 ± SD)	26.3±3.6	22.1±1.8	34.1± 5.7	F: 311.8	**<0.0001**
Primary Psychiatric Diagnosis (N, %)					
Schizophrenia	53 (41.7)	35(42.2)	18 (40.9)	χ^2: 0.02	0.89
Bipolar Disorder	23 (18.1)	18 (21.7)	5 (11.4)	χ^2: 2.07	0.15
Depressive Disorders	32 (25.2)	24 (28.9)	8 (18.2)	χ^2: 1.76	0.18
Substance Use Disorder [c]	7 (5.5)	1 (1.2)	6 (13.6)	χ^2: 8.53	**0.0035**
Dementia	3 (2.4)	1 (1.2)	2 (4.5)	χ^2: 1.39	0.24
Other	9 (7.1)	4 (4.8)	5 (11.4)	χ^2: 1.87	0.17
Antipsychotic Treatment (N, %)					
Olanzapine	41 (32.3)	24 (28.9)	17 (38.6)	χ^2: 1.24	0.26
Quetiapine	36 (28.3)	29 (34.9)	7 (15.9)	χ^2: 5.13	**0.024**
Risperidone	36 (28.3)	22 (26.5)	14 (31.8)	χ^2: 0.40	0.43
Aripiprazole	11 (8.7)	6 (7.2)	5 (11.4)	χ^2: 0.62	0.62
Ziprasidone	12 (9.4)	9 (10.8)	3 (6.8)	χ^2: 0.54	0.46
Clozapine	7 (5.5)	3 (3.6)	4 (9.1)	χ^2: 1.66	0.20
First-generation antipsychotic	5 (3.9)	1 (1.2)	4 (9.1)	χ^2: 4.73	**0.030**
Antipsychotic Polytherapy	20 (15.7)	12 (14.5)	8 (18.2)	χ^2: 0.30	0.58

Characteristic	Total [a] (N=127)	Normal Weight (BMI=18.5–24.9) (N=83)	Obese (BMI ≥ 30) (N=44)	F / chi^2	P-value
Non-antipsychotic Treatment (N, %)					
Anxiolytics/Hypnotics (N, %)	70 (55.1)	47 (56.6)	23 (52.3)	χ^2: 0.22	0.64
Antidepressants (N, %)	63 (49.6)	42 (50.6)	21 (47.7)	χ^2: 0.09	0.76
Mood Stabilizers (N, %)	42 (33.1)	30 (36.1)	12 (27.3)	χ^2: 1.02	0.31
Anticholinergics (N, %)	8 (6.3)	6 (7.2)	2 (4.5)	χ^2: 0.35	0.55

Bolded p-values <.05. FGA: First-generation antipsychotic; SGA: Second-generation antipsychotic

[a]Total number of patients reduced by those receiving lipid lowering, antihyperglycemic or antihypertensive medications, i.e., obese patients without MetS: N=5, normal weight patients without MetS: N=4)

[b]Based on ethnic/racial information from 82 normal weight patients and 43 obese patients

[c]Number of patients with a substance use disorder as the primary or secondary diagnosis: N=25

Table 2

Metabolic Variables at Time of Psychiatric Admission in Normal Weight and Obese Patients Without Metabolic Syndrome

Metabolic Variables	Total [a] (N=127)	Normal Weight (BMI=18.5–24.9) (N=83)	Obese (BMI ≥ 30) (N=44)	F / chi^2	P-value	Adjusted P-value [b]
Categorical Metabolic Syndrome Criteria						
# of Metabolic Syndrome Criteria (±SD)	1.1±0.71	0.91±0.74	1.36±0.65	F: 11.44	**0.0010**	**0.0029**
Waist circumference >40 inches in males, >35 inches in females	18 (14.3)	2 (2.4)	16 (36.4)	χ^2: 26.91	**<0.0001**	**0.0004**
Fasting glucose ≥100 mg/dL (N, %)	17 (13.5)	12 (14.6)	5 (11.4)	χ^2: 0.26	0.61	0.86
Blood pressure ≥ 130/85 (N, %)	34 (27.0)	20 (24.4)	14 (31.8)	χ^2: 0.80	0.37	0.50
HDL-Cholesterol <40 mg/dl in males or <50 mg/dl in females (N, %)	48 (38.1)	29 (35.4)	19 (43.2)	χ^2: 0.74	0.39	0.44
Triglycerides ≥150 mg/dL (N, %)	18 (14.4)	13 (16.1)	5 (11.4)	χ^2: 0.51	0.48	0.91
Continuous Metabolic Syndrome Criteria						
Waist circumference (cm ± SD)	86.8±11.2	81.3±6.6	97.0±16.8	F: 55.75	**<0.0001**	**<0.0001**
Fasting glucose (mg/dL ± SD) [c]	86.0±14.5	86.8±15.5	84.4±12.3	F: 0.77	0.38	0.33
Systolic blood pressure (mm Hg ± SD)	120.0±12.5	118.6±13.6	122.7±10.3	F: 3.04	0.083	0.17
Diastolic blood pressure (mm Hg ± SD)	77.6±8.2	76.1±8.5	80.4±7.6	F: 7.62	**0.0066**	**0.0078**
Triglycerides (mg/dL ± SD) [c]	99.5±48.2	99.2±50.3	100.0±43.8	F: 0.0071	0.93	0.45
HDL-Cholesterol (mg/dl ±SD)	47.9.4±10.5	49.2±10.2	45.6±11.1	F: 3.30	0.072	0.24
Additional Continuous Lipid Parameters						
Total Cholesterol (mg/dL ± SD)	166.8±36.1	165.3±37.4	169.5±33.6	F: 0.38	0.54	0.22
LDL-Cholesterol (mg/dL ± SD)	112.7±35.6	109.6±36.7	118.5±33.2	F: 1.77	0.18	**0.046**
Non-HDL-Cholesterol (mg/dL ± SD)	119.7±35.8	117.5±37.2	123.9±32.9	F: 0.92	0.34	0.10
10-Year Coronary Heart Disease Risk						
10-year CHD Risk (% ± SD) [c]	2.5±4.2	2.6±4.6	2.3±3.5	F: 0.17	0.68	0.87
- Males	3.4±5.1	2.8±3.4	3.8±5.9	F: 0.59	0.45	0.34
- Females	1.6±2.9	1.5±2.5	1.7±3.7	F: 0.044	0.83	0.28
- 10-year CHD Risk (% ± SD) in patients with abdominal obesity [c]	2.6±4.4	2.6±4.6	2.5±3.6	F: 0.24	0.88	0.64

Metabolic Variables	Total [a] (N=127)	Normal Weight (BMI=18.5–24.9) (N=83)	Obese (BMI ≥ 30) (N=44)	F / chi^2	P-value	Adjusted P-value [b]
- 10-year CHD Risk (% ± SD) in patients without abdominal obesity [c]	1.9±3.4	2.0±1.4	1.9±3.5	F: 0.0006	0.98	0.74

[a] Total number of patients reduced by those receiving lipid lowering, antihyperglycemic or antihypertensive medications, i.e., obese patients without MetS: N=5, normal weight patients without MetS: N=4)

[b] Adjusted for Caucasian race, smoking status, substance use disorder diagnosis, quetiapine use and FGA cotreatment, variables that in univariate analyses differed between the two groups at p<0.1, except for BMI (see Table 1).

[c] Based on data from 82 normal weight and 44 obese patients