BIPOLAR DISORDERS
AN INTERNATIONAL JOURNAL OF PSYCHIATRY AND NEUROSCIENCES

Bipolar Disorders 2014: 16: 277–288

Original Article

Metabolic syndrome in bipolar disorder and schizophrenia: dietary and lifestyle factors compared to the general population

Bly MJ, Taylor SF, Dalack G, Pop-Busui R, Burghardt KJ, Evans SJ, McInnis MI, Grove TB, Brook RD, Zöllner SK, Ellingrod VL. Metabolic syndrome in bipolar disorder and schizophrenia: dietary and lifestyle factors compared to the general population. Bipolar Disord 2014: 16: 277–288. © 2013 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd.

Objective: Since a poor diet is often cited as a contributor to metabolic syndrome for subjects diagnosed with bipolar disorder and schizophrenia, we sought to examine dietary intake, cigarette smoking, and physical activity in these populations and compare them with those for the general population.

Methods: Individuals diagnosed with bipolar disorder (n = 116) and schizophrenia (n = 143) were assessed for dietary intake, lifestyle habits, and metabolic syndrome and compared to age-, gender-, and race-matched subjects from the National Health and Nutrition Examination Survey (NHANES) 1999–2000. Additionally, matched subgroups within the patient populations were compared to elicit any differences.

Results: As expected, the metabolic syndrome rate was higher in the samples with bipolar disorder (33%) and schizophrenia (47%) compared to matched NHANES controls (17% and 11%, respectively), and not different between the patient groups. Surprisingly, both subjects with bipolar disorder and those with schizophrenia consumed fewer total calories, carbohydrates and fats, as well as more fiber ($p < 0.03$), compared to NHANES controls. No dietary or activity differences between patient participants with and without metabolic syndrome were found. Subjects with schizophrenia had significantly lower total and low-density cholesterol levels ($p < 0.0001$) compared to NHANES controls. Subjects with bipolar disorder smoked less ($p = 0.001$), exercised more ($p = 0.004$), and had lower body mass indexes ($p = 0.009$) compared to subjects with schizophrenia.

Conclusions: Counter to predictions, few dietary differences could be discerned between schizophrenia, bipolar disorder, and NHANES control groups. The subjects with bipolar disorder exhibited healthier behaviors than the patients with schizophrenia. Additional research regarding metabolic syndrome mechanisms, focusing on non-dietary contributions, is needed.

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doi: 10.1111/bdi.12160

Key words: atypical antipsychotics – bipolar disorder – dietary intake – metabolic syndrome – schizophrenia

Received 5 November 2012, revised and accepted for publication 1 August 2013

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Clinical Trials Identifier: NCT00815854, Grants.gov.

The relationships between cardiovascular disease and medication use for those diagnosed with bipolar disorder and schizophrenia are gaining increasing attention. In looking at our previous work as well as other reports in the literature, we found that approximately 40% of those with a serious mental illness met National Cholesterol Education Panel-Adult Treatment Panel III (NCEP-ATP-III) guidelines for metabolic syndrome (1–6). Many groups have suggested a

pharmacogenetic risk for metabolic syndrome (5–7). However, a poor diet and unhealthy lifestyle choice, such as cigarette smoking and lack of physical activity, are major cardiovascular disease contributors and often seen in patients with a serious mental illness (8–11). While the literature examining relationships between diet, lifestyle, and cardiovascular disease within the general population is broad, little has been done among those with serious mental illness. For these individuals, up to 30 years of life are lost due to cardiovascular disease (12). This may be due to the higher rate of metabolic syndrome (~40%) within this group (1). Thus, in addition to understanding the medication and genetic risks associated with cardiovascular disease in mental health disorders, understanding overall dietary and lifestyle characteristics within populations with a serious mental illness is critical to prevent premature death and develop individualized interventions to prevent metabolic syndrome. In order to do this, a thorough understanding of the dietary and lifestyle habits for each of these groups is needed (13).

Thus, the primary aim of this study was to examine dietary intake in community-dwelling subjects diagnosed with bipolar disorder and schizophrenia compared to that for the general population using age-, race-, and gender-matched subjects from the National Health and Nutrition Examination Survey (NHANES) 1999–2000 data. For this investigation, we also decided to specifically focus on the intake of the essential fatty acids (EFAs), since our group reported that atypical antipsychotics may neutralize the cardiovascular benefits of omega 3 fatty acid intake (14); however, EFA intake in schizophrenia is particularly understudied, as is the general study of dietary intake within this population. Our secondary aim was to examine differences between age-, race-, and gender-matched subjects with bipolar disorder and schizophrenia in regard to dietary intake (both general dietary intake and dietary intake related to EFAs), as well as lifestyle behaviors (smoking and exercise) and their relationship to metabolic syndrome. Our hypothesis was that NHANES subjects, matched on age, race, and gender, would display healthier dietary choices compared to those with a serious mental illness. We also hypothesized that the matched bipolar disorder and schizophrenia groups would have few differences in dietary intake and lifestyle behaviors. Lastly, we hypothesized that subjects meeting metabolic syndrome criteria would have poorer overall and EFA-specific dietary intake, increased rates of smoking and low physical activity compared to those without metabolic syndrome.

Methods

Study subjects with bipolar disorder and schizophrenia

Subjects in this analysis met the following inclusion criteria: (i) DSM-IV diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, or bipolar disorder type I or type II; (ii) ≥18 years of age; and (iii) pharmacologic mental health treatment for at least six months. Subjects were excluded if they: (i) were unable to provide informed consent (assessed using a short questionnaire asking key questions about the study); (ii) had documented type II diabetes before antipsychotic treatment started; or (iii) had a documented active substance abuse diagnosis. The inclusion and exclusion criteria for this study were broad in an effort to represent 'real world' practice. These criteria did not include any additional medical-related inclusion or exclusion criteria. Study subjects were recruited from ambulatory care mental health clinics and were included in a previous pharmacogenomics study related to the occurrence of atypical antipsychotic-associated metabolic complications (5) as well as in the Prechter Longitudinal Study of Bipolar Disorder (15). The study protocols were approved by the University of Michigan Medical School Institutional Review Board (IRBMED) and informed consent was obtained from all subjects.

National Health and Nutrition Examination Survey (NHANES) subject data

Age- (within three years), race-, and gender-matched controls from the general population for each subject were obtained through the National Health and Nutrition Examination Survey (NHANES) 1999–2000 database (16). From this database, we extracted data related to dietary intake, laboratory values, and demographics in order to compare the NHANES subjects with the matched subjects with bipolar disorder and schizophrenia. We were unable to match the subjects with bipolar disorder and schizophrenia with the NHANES controls in regard to education, years of employment, living situation, or socioeconomic status.

Assessments

Subjects with bipolar disorder and schizophrenia meeting inclusion and exclusion criteria underwent a procedure to obtain informed consent, including a brief assessment of the risks and benefits associated with study participation. After consent had been obtained, a clinical interview, which included

the Structured Clinical Interview for DSM diagnoses (SCID) for patients with schizophrenia (17) or the Diagnostic Interview for Genetic Studies (DIGS) for the subjects with bipolar disorder (18), was completed by a trained research assistant to confirm the psychiatric diagnosis. Different diagnostic instruments were used since the patients came from two different primary studies, although the procedures used for gathering all other data were identical across subject groups. Subjects underwent a thorough assessment of current and past medication history which was confirmed by medical record review. This information was used to calculate overall antipsychotic exposure using chlorpromazine equivalents (19). Our primary atypical antipsychotic (AAP) group included those receiving olanzapine, clozapine, quetiapine, risperidone, and paliperidone, similar to our previous investigations (5, 6, 14). Ziprasidone and aripiprazole were not included in the primary classification due to their reduced potential to cause weight gain and metabolic syndrome; however, our secondary analysis did include these two medications as atypical antipsychotics (20).

Subjects fasted (for >8 hours) before the study visits, which took place between 8 a.m and noon, or within two hours of their usual waking time based on appointment availability. Vital signs (i.e., height and weight) and hip and waist circumferences were measured for each subject and body mass index (BMI) was calculated.

Subjects diagnosed with bipolar disorder or schizophrenia recalled all foods eaten for the previous 24 hours prior to fasting, and this was repeated twice within the next 10 days for a total of three assessments. The methods used to conduct this assessment were identical to the 24-hour food recount conducted as part of the NHANES study (see http://www.cdc.gov/nchs/tutorials/dietary/surveyorientation/dietarydataoverview/info2.htm for additional information regarding this assessment). For both our study and the NHANES study, a standardized script was used during an in-person interview. This was then repeated by telephone once more for the NHANES study and twice more for our studies within 10 days after the initial interview. Our assessments were administered by the registered dieticians from the Michigan Clinical Research Unit (MCRU) using a standardized protocol outlined on the NHANES tutorial and included using standard measuring guides as tools to help subjects accurately report the volume and dimensions of foods consumed in the previous 24 hours. This standardized assessment has been used extensively within the dietary literature and provides high-quality intake data with minimal bias (21–23). The 24-hour recall has become the preferred tool for monitoring diets of various populations for the study of disease and diet associations (24) and has been previously used in different schizophrenia populations (25). Data obtained from these recalls from both our studies as well as the NHANES dataset were then used to calculate average calorie intake using the Nutrition Data Systems for Research (NDSR) software developed by the Nutrition Coordinating Center (NCC) at the University of Minnesota (26). The output from these analyses was averaged over the two recalls for the NHANES controls and three recalls for the subjects with bipolar disorder and schizophrenia. This output provides values for more than 140 nutrients, nutrient ratios, and other compounds based on the information gathered. Based on our previous finding that atypical antipsychotics may blunt the cardio-protective effects of omega 3 fatty acids (14), we chose to focus on dietary intake related to essential fatty acids [omega 3 fatty acids (N-3) and omega 6 fatty acids (N-6)], the N-3/N-6 ratio, total fat, and saturated fatty acids (SFAs), and polyunsaturated fat acids (PUFAs). We also included more general measurements of caloric intake such as total calories, carbohydrates, dietary fiber, and glycemic index in an effort to understand overall dietary intake.

The smoking and physical activity assessments for the subjects with bipolar disorder and schizophrenia consisted of questions about smoking (number of cigarettes smoked per day, age when smoking stated, and quit date if applicable) to calculate a smoking pack-year history. An assessment of average physical activity was also obtained using the Total Activity Measure 2 (TAM2) which measures total or moderate-intensity physical activity for participants and has been validated against RT3 triaxial accelerometer measurements in a population with coronary heart disease (27). A higher score indicates greater physical activity over the past week and the score is reported in metabolic equivalent (MET)/min. Data related to these lifestyle assessments were not available for the NHANES controls.

Blood was obtained from fasting subjects with bipolar disorder and schizophrenia for the following assessments: glucose, insulin, hemoglobin A1c, and lipids [total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL)]. Subjects were determined to have a diagnosis of metabolic syndrome using the NCEP-ATP III guidelines (3), based on the results of the laboratory and clinical measurements. Metabolic syndrome is defined as having any three of the following: (i) abdominal obesity

characterized by waist circumference of >40 inches for men and >35 inches for women; (ii) triglycerides ≥150 mg/dL; (iii) HDL cholesterol <40 mg/dL for men and <50 mg/dL for women or receiving a lipid-lowering agent; (iv) blood pressure ≥130/≥85 mmHg or treatment for hypertension; or (v) fasting glucose ≥100 mg/dL or treatment of diabetes. Insulin resistance was calculated using the homeostasis model assessment–insulin resistance (HOMA-IR). Data on these laboratory values for control subjects were obtained through NHANES (16).

Statistical analysis

All analyses were conducted using JMP version 8 or 9 (SAS Institute, Cary, NC, USA). For our primary aim, we examined differences between the subjects with bipolar disorder or schizophrenia compared to NHANES matched subjects on race, gender, and age (within three years). For our second analysis, we were interested in determining differences between the subjects with bipolar disorder and schizophrenia, and thus subjects within these two groups were also matched by race, gender, and age (within three years), resulting in a smaller subset of these patients being included in this analysis.

Differences for the primary outcomes and sociodemographic variables between diagnostic and metabolic syndrome groups were determined by the use of one-way analysis of variance (ANOVA) for normally distributed variables (BMI, waist circumference, age, metabolic measures, dietary intake, and the physical activity assessment). Chi-squared analyses compared dichotomous variables (e.g., gender, smoking status, and atypical antipsychotic use) by diagnostic and metabolic syndrome groups. Our dietary analysis using the NDSR database resulted in a plethora of information. As stated above, we decided *a priori* to focus on dietary intake measures of approximately 10 different values for our initial analysis, since our previous work has shown a relationship between omega 3 fatty acid intake, atypical antipsychotic use, and endothelial functioning (14). These values are listed in Tables 1 and 2 and discussed below. A general linear regression was performed to determine dietary and lifestyle predictors of metabolic syndrome using metabolic syndrome (and its individual components) as the dependent variables, and age, race, gender, AAP use, and dietary and lifestyle measurements as independent variables. A p-value less than 0.05 was considered statistically significant due to the exploratory nature of this investigation.

Results

Characteristics of subjects diagnosed with bipolar disorder or schizophrenia, and NHANES controls

A total of 143 subjects with schizophrenia, 116 subjects with bipolar disorder, and 259 age- (within three years), gender-, and race-matched subjects from NHANES (1999–2000) were included (16). Table 1 outlines group characteristics. In general, 47% of our schizophrenia group and 33% of our bipolar disorder group met criteria for metabolic syndrome; the difference was not statistically different ($p = 0.52$). These rates are significantly higher than those seen in the NHANES controls (11% and 17% for those matched to subjects in the schizophrenia and bipolar disorder groups, respectively) as well as the 20–25% rate reported in the literature (Table 1). Both the bipolar disorder and schizophrenia groups had differences in most metabolic measures (i.e., higher BMI, blood pressure, and glucose) compared to the NHANES subjects. Interestingly, the schizophrenia group had significantly lower lipid measurements compared to the NHANES subjects (total cholesterol 169 mg/dL versus 196 mg/dL, respectively, $p < 0.0001$), while no differences were found for the bipolar disorder group compared to the NHANES subjects (191 mg/dL versus 188 mg/dL, respectively, $p = 0.51$).

Dietary differences between the mental illness groups and the NHANES subjects are detailed in Table 2. In general, both the bipolar disorder and schizophrenia groups reported consuming significantly less calories ($p = 0.031$) and less carbohydrates ($p < 0.0001$) than NHANES subjects. The bipolar disorder group also reported a significantly lower intake of saturated fatty acids ($p = 0.007$), fat in general ($p = 0.048$) and monounsaturated fatty acids ($p = 0.03$). No other differences were found in the average dietary intake for either the bipolar disorder or schizophrenia group compared to the NHANES subjects. However, the omega 6 to omega 3 (N-6/N-3) ratio for the NHANES subjects was significantly higher than that for the subjects with schizophrenia ($p = 0.02$), although for the schizophrenia and bipolar disorder groups and their matched NHANES groups, this ratio was around 10, which is above the recommended intake ratio of one to four (28).

Differences between matched subjects with bipolar disorder and schizophrenia

In order to determine disease-specific differences in diet and lifestyle factors that may affect metabolic syndrome occurrence, a subset of our subjects with

Table 1. Differences in laboratory and dietary measures between age-, race-, and gender-matched patients with schizophrenia and bipolar disorder, and general population controls

Measurement	Schizophrenia (n = 143)	NHANES matches (n = 143)	p-value
Age, years	45.8 (11.2)	45.9 (11.2)	1
Race, Caucasian/ African American, %	61/30	61/30	1
Gender, male/female, %	64/36	64/36	1
Meeting metabolic syndrome, %	47	11	<0.0001
BMI, kg/m^2	33.0 (8.2)	26.6 (6.6)	<0.0001
Systolic BP, mm Hg	124.6 (17.1)	122.3 (21.3)	0.0052
Diastolic BP, mm Hg	75.9 (12.7)	70.8 (14.3)	0.0012
Homocysteine, μmol/L	11.4 (5.0)	6.5 (2.5)	<0.0001
Total cholesterol, mg/dL	169.0 (42.7)	196.4 (44.4)	<0.0001
HDL, mg/dL	50.1 (15.7)	50.5 (13.6)	0.85
LDL, mg/dL	101.0 (31.7)	127.4 (48.7)	<0.0001
Triglycerides, mg/dL	137.5 (101.5)	127.7 (76.3)	0.61
Blood glucose, mg/dL	107.3 (53.3)	88.6 (18.4)	<0.0001
HOMA-IR	6.6 (6.2)	3.3 (2.8)	<0.0001
Measurement	Bipolar disorder (n = 116)	NHANES matches (n = 116)	
Age, years	43.3 (12.1)	42.5 (12.2)	1
Race, Caucasian/ African American, %	82/11	82/11	1
Gender, male/female, %	34/66	34/66	1
Meeting metabolic syndrome, %	33	17	<0.0001
BMI, kg/m^2	32.3 (8.7)	25.4 (5.9)	<0.0001
Systolic BP, mm Hg	123.6 (18.1)	116.6 (16.7)	0.58
Diastolic BP, mm Hg	73.0 (10.9)	69.9 (13.0)	0.07
Homocysteine, μmol/L	10.5 (3.3)	6.6 (2.7)	<0.0001
Total cholesterol, mg/dL	191.5 (44.9)	187.7 (40.9)	0.51
HDL, mg/dL	57.4 (15.1)	50.5 (13.4)	0.0005
LDL, mg/dL	118.2 (38.4)	111.3 (30.1)	0.23
Triglycerides, mg/dL	146.4 (106.3)	155.2 (158.8)	0.62
Blood glucose, mg/dL	101.9 (31.1)	91.0 (14.0)	0.018
HOMA-IR	8.2 (13.1)	3.4 (3.1)	<0.0001

Values are presented as mean (standard deviation) unless noted otherwise. BMI = body mass index; BP = blood pressure; HDL = high-density lipoprotein; HOMA-IR = Homeostasis Model of Assessment–Insulin Resistance; LDL = low-density lipoprotein; NHANES = National Health and Nutrition Examination Survey.

Table 2. Comparison of dietary and lifestyle variables between groups: comparison of dietary intake and lifestyle measures between age-, race-, and gender-matched patients with schizophrenia and bipolar disorder, and National Health and Nutrition Examination Survey (NHANES) matches

Measurement (consumed)	Schizophrenia (n = 143)	NHANES matches (n = 143)	p-value
Energy, kcal/day	2,072 (736)	2,291 (1,084)	0.031
Carbohydrates, g/day	260.9 (100.6)	294.0 (151.7)	0.037
Saturated fatty acids, g/day	28.3 (11.8)	28.5 (17.8)	0.89
Fiber, g/day	17.2 (9.0)	12.2 (8.8)	<0.0001
Fat, g/day	81.4 (33.1)	85.4 (49.0)	0.39
Polyunsaturated fatty acids, g/day	17.1 (9.4)	17.8 (11.6)	0.57
Protein, g/day	79.0 (32.9)	82.0 (43.4)	0.47
Monounsaturated fatty acids, g/day	29.3 (12.7)	32.6 (19.6)	0.08
Omega 3 fatty acids, g/day	1.7 (0.9)	1.7 (1.3)	0.94
Omega 6 fatty acids, g/day	16.9 (9.3)	16.8 (11.8)	0.98
Omega 6/ omega 3 ratio	10.8 (3.8)	13.0 (13.7)	0.02
Measurement (consumed)	Bipolar disorder (n = 116)	NHANES matches (n = 116)	
Energy, kcal/day	1,896 (609)	2,309 (1,021)	0.0005
Carbohydrates, g/day	241.0 (92.2)	300.5 (172.6)	0.0007
Saturated fatty acids, g/day	24.4 (11.9)	29.6 (16.2)	0.0073
Fiber, g/day	19.0 (10.2)	14.7 (9.7)	0.0007
Fat, g/day	74.3 (31.2)	84.7 (41.3)	0.048
Polyunsaturated fatty acids, g/day	16.6 (7.5)	16.7 (9.9)	0.96
Protein, g/day	73.3 (22.9)	82.3 (38.8)	0.056
Monounsaturated fatty acids, g/day	27.3 (12.8)	31.8 (16.6)	0.030
Omega 3 fatty acids, g/day	1.8 (0.9)	1.6 (1.1)	0.16
Omega 6 fatty acids, g/day	16.3 (7.5)	16.5 (10.0)	0.86
Omega 6/ omega 3 ratio	9.9 (4.2)	10.8 (3.1)	0.38

Values are presented as mean (standard deviation).

bipolar disorder and schizophrenia were also matched by race, gender, and age (within three years), resulting in 78 matches for a final sample size of 156. A total of 103 subjects (65 from the schizophrenia group and 38 from the bipolar disorder group) did not have a match and were excluded from this analysis. The mean ± standard deviation age of this group was 45.1 ± 10.9 years, and 60% were female, 80% were Caucasian, and 13% were African American. A description of demographic,

dietary, lifestyle, and metabolic differences between the patients with bipolar disorder and schizophrenia is given in Table 3.

Similar to the previous analysis, we examined differences in both metabolic measures and dietary intake. There was a significant difference between the two groups related to cholesterol, as the bipolar disorder group had higher total cholesterol measurements (194 mg/dL versus 174 mg/dL, respectively, p = 0.009) and LDL cholesterol measurements (120.3 mg/dL versus 102.7 mg/dL, respectively, p = 0.005) compared to subjects with schizophrenia. We had hypothesized that this might be due to a difference in lipid-lowering medications between these groups, but as can be seen from Table 3, this was not the case, as use of these medications in general was low overall (25%). For other metabolic indices, there were no statistically significant differences in fasting glucose (p = 0.67), insulin resistance (HOMA-IR, p = 0.35) blood pressure (p = 0.63), or BMI (p = 0.13) between the two groups, and both groups met criteria for obesity (BMI > 30 mm/kg^2). In terms of central adiposity, the schizophrenia group had a much lower hip/waist ratio compared to those with bipolar disorder (p = 0.02), suggesting greater central adiposity for those with schizophrenia (11). Additionally, the rate of AAP use among the bipolar disorder

Table 3. Description of demographic, dietary intake, and metabolic differences between age-, race-, and gender-matched patients with schizophrenia and bipolar disorder

Variable	Schizophrenia (n = 78)	Bipolar disorder (n = 78)	p-value
Demographics			
Age, years, mean (SD)	45.1 (10.9)	46.1 (10.9)	0.59
Race, Caucasian/African American, %	77/17	84/12	0.29
Gender, male, %	40	40	1
Atypical antipsychotic use, %	74	53	0.009
Metabolic parameters			
BMI, kg/m^2, mean (SD)	34.1 (8.7)	32.1 (7.7)	0.13
Hip/waist ratio, mean (SD)	1.05 (0.09)	1.09 (0.11)	0.02
Systolic BP, mmHg, mean (SD)	122 (18)	124 (19)	0.63
Diastolic BP, mmHg, mean (SD)	74 (12)	74 (11)	0.98
Homocysteine, μmol/L, mean (SD)	11.3 (6.0)	10.8 (3.4)	0.64
Total cholesterol, mg/dL, mean (SD)	173.9 (46.2)	194.5 (49.3)	0.009
HDL, mg/dL, mean (SD)	54.5 (17.5)	56.7 (16.0)	0.43
LDL, mg/dL, mean (SD)	102.7 (33.4)	120.3 (41.8)	0.005
Triglycerides, mg/dL, mean (SD)	134.9 (101.7)	160.2 (111.3)	0.15
Glucose, mg/dL, mean (SD)	107.2 (46.6)	104.4 (36.7)	0.67
Meeting ATP-III metabolic syndrome criteria, %	42	37	0.52
HOMA-IR, mean (SD)	6.7 (6.9)	8.7 (16.1)	0.35
Dietary and lifestyle parameters			
Current smoker, %	70	45	0.001
Total activity score (TAM2), MET/min, mean (SD)	2,423 (2,492)	4,027 (4,096)	0.004
Total calories, kcal/day, mean (SD)[a]	1,990 (735)	1,953 (656)	0.74
Carbohydrates, kcal/day, mean (SD)[a]	250 (100)	246 (96)	0.82
Total fat, g/day, mean (SD)[a]	79 (35)	77 (34)	0.71
PUFA, g/day, mean (SD)[a]	17 (10)	17 (8)	0.96
SFA, g/day, mean (SD)[a]	29 (12)	26 (13)	0.30
Dietary fiber, g/day, mean (SD)[a]	18 (10)	18 (9)	0.71
Glycemic index (glucose reference), mean (SD)	59.4 (4.9)	60.2 (7.4)	0.39
Omega 3 fatty acids, g/day, mean (SD)[a]	1.9 (0.9)	1.8 (1.0)	0.16
Omega 6 fatty acids, g/day, mean (SD)[a]	16.6 (9.7)	16.6 (7.9)	0.98
Omega 6/omega 3 ratio, mean (SD)	11.1 (4.3)	10.1 (4.7)	0.17
Medications			
Cumulative chlorpromazine equivalents, mg, mean (SD)	439.7 (326.8)	247.4 (308.2)	0.0002
Mood stabilizer, %[b]	30	79	<0.0001
Antidepressant, %[b]	54	60	0.42
Anti-hypertensive, %[b]	31	28	0.73
Lipid lowering medication, %[b]	29	22	0.27
Oral hypoglycemic medication, %[b]	15	6	0.22

BMI = body mass index; BP = blood pressure; HDL = high-density lipoprotein; HOMA-IR = Homeostasis Model of Assessment–Insulin Resistance; LDL = low-density lipoprotein; PUFA = polyunsaturated fatty acids; SD = standard deviation; SFA = saturated fatty acids.
[a]Amount consumed per day.
[b]Current medication.

and schizophrenia groups was different. Seventy-four percent of those with schizophrenia and 53% of those with bipolar disorder were receiving an AAP at the time of assessment, and those with schizophrenia had a higher overall chlorpromazine equivalent measurement ($p = 0.0002$), which is in line with the first-line treatments for each of these serious mental illnesses. As previously stated, as part of our primary analysis we did not include subjects taking the medications aripiprazole or ziprasdone within the AAP group due to a lower reported propensity for weight gain and other metabolic consequences (29). When these medications were included in our secondary analysis of AAP classification, 80% of the subjects with bipolar disorder and 84% of the subjects with schizophrenia were receiving AAPs, a difference that was not statistically significant ($p = 0.22$). We also compared the use of other psychotropic medications between the two groups and found more mood stabilizer usage within the bipolar disorder group (79% versus 30%, respectively, $p < 0.0001$); however, no differences were seen in regard to antidepressant, antihypertensive, oral hypoglycemic, and lipid-lowering agent usage ($p > 0.20$ for all).

In addition to the laboratory differences between the two groups, no differences in dietary intake were noted between the matched bipolar and schizophrenia groups, as outlined in Table 3. Given the previous relationship we reported between AAP use and omega 3 fatty acid dietary consumption, we wanted to examine essential fatty acid intake among these groups. Most notably, mean omega 3 fatty acid (N-3) intake was 1.8 g/day, which is within the recommended consumption of 1–2 g/day (30); however, the ratio of omega 6 to omega 3 fatty acids (N-6/N-3) was approximately 10 for each group, and current recommendations are to maintain a ratio of around 1 to 4 for optimal cardiovascular health (31). In terms of other lifestyle differences, the bipolar disorder population displayed healthier choices than the schizophrenia group in that fewer of them smoked cigarettes (45% versus 70%, respectively, $p = 0.001$) and they reported more physical activity ($p = 0.004$). Thus, despite reporting overall healthier lifestyle choices, and having healthier diets and lower AAP use compared to the subjects with schizophrenia, those with bipolar disorder still were at an increased risk for metabolic syndrome.

Metabolic syndrome differences

For this analysis, the above mentioned age-, race-, and gender-matched subjects with bipolar disorder and schizophrenia were stratified by metabolic syndrome criteria (32). Group differences are outlined in Table 4. Those with metabolic syndrome were slightly older than those without metabolic syndrome (mean age 48 versus 43 years old, respectively, $p = 0.004$), with no differences in race, gender, or the percentage who smoked cigarettes. Additionally, within both groups, approximately 60% reported AAP use (68% versus 57%, respectively, $p = 0.17$); however, antidepressant use was higher in the metabolic syndrome group (69% versus 49%, respectively, $p = 0.01$). When the predetermined dietary variables of interest were examined, no differences were found. Thus, despite meeting criteria for metabolic syndrome, the diet and lifestyle choices of those classified as having metabolic syndrome appeared to be very similar to those of subjects not meeting metabolic syndrome criteria.

For our regression model, we examined the relationship between metabolic syndrome and the dietary and lifestyle parameters outlined in Table 4. None of the dietary and lifestyle parameters were specifically associated with metabolic syndrome, except antidepressant use ($\chi^2 = 9.46$, $p = 0.002$), which remained significant after controlling for age ($\chi^2 = 5.54$, $p = 0.02$). In fact, the odds ratio for metabolic syndrome in antidepressant users was 2.24 (95% confidence interval: 1.33–14.9).

Discussion

Overall, our study found metabolic differences between patients with bipolar disorder or schizophrenia and NHANES controls, which was not surprising given extensive previous work (1, 33–36). Contrary to expectations, the subjects with bipolar disorder and schizophrenia showed similar or better dietary intake than the NHANES subjects, and for those with a serious mental illness, dietary, smoking, and physical activity measurements did not distinguish those with and without metabolic syndrome, except for the use of antidepressants. Subjects with schizophrenia showed lower total and LDL cholesterol levels, compared to NHANES subjects, which is somewhat contradictory to the existing hypotheses around AAP use, lipid biosynthesis, and lipid utilization within the schizophrenia population (37). While these findings appear to contradict the received wisdom about metabolic syndrome, we believe that they actually provide an important insight into a major health risk factor that might not be as straightforward as it seems.

It is widely assumed that metabolic syndrome is largely associated with poor dietary habits, and

Table 4. Description of demographic, dietary intake, and metabolic differences between age-, race-, and gender-matched patients with schizophrenia and bipolar disorder with and without metabolic syndrome

Variable	With metabolic syndrome (n = 62)	Without metabolic syndrome (n = 94)	p-value
Demographics			
Age, years, mean (SD)	48.7 (9.7)	43.5 (11.1)	0.004
Race, Caucasian/ African American, %	83/12	79/16	0.92
Gender, male, %	60	60	0.90
Schizophrenia/ bipolar disorder, %	47/53	52/47	0.51
Atypical antipsychotic use, %	68	57	0.17
Cumulative chlorpromazine equivalents, mg, mean (SD)	438.7 (439.0)	401.9 (379.1)	0.58
Mood stabilizer, %[a]	55	55	0.95
Antidepressant, %[a]	69	49	0.01
Dietary and lifestyle parameters			
Current smoker, %	53	41	0.15
Total calories, kcal/day, mean (SD)[b]	1,973.9 (657.6)	1,973.2 (737.5)	0.96
Total activity score (TAM2), MET/min, mean (SD)	2,902 (2,797)	3,738 (3,856)	0.35
Carbohydrates, kcal/day, mean (SD)[b]	245.2 (92.9)	251.0 (101.1)	0.72
SFA, g/day, mean (SD)[b]	27.5 (13.5)	26.5 (12.6)	0.63
Dietary fiber, g/day, mean (SD)[b]	17.8 (8.9)	18.2 (9.5)	0.83
Total fat, g/day, mean (SD)[b]	79.9 (34.8)	77.7 (34.5)	0.69
PUFA, g/day, mean (SD)[b]	16.6 (9.1)	16.9 (8.7)	0.85
Vitamin D, μg/day, mean (SD)[b]	7.7 (7.7)	7.4 (12.7)	0.87
Glycemic index (glucose reference), mean (SD)	59.7 (4.8)	59.8 (7.1)	0.93
Omega 3 fatty acids, g/day, mean (SD)[b]	1.6 (0.9)	1.8 (1.0)	0.38
Omega 6 fatty acids, g/day, mean (SD)[b]	16.3 (8.9)	16.7 (8.7)	0.80
Omega 6/omega 3 ratio, mean (SD)	11.0 (4.4)	10.4 (4.6)	0.64

PUFA = polyunsaturated fatty acids; SD = standard deviation; SFA = saturated fatty acids.
[a]Current medication.
[b]Amount consumed per day.

while the literature shows ample support for this thesis in the population at large (38), this has been remarkably under-investigated in those with serious mental illness. Our bipolar and schizophrenia groups exhibited few dietary differences compared to the NHANES subjects. In fact, both of our patient groups consumed fewer calories and more fiber and few carbohydrates compared to controls. Thus, these data directly contradict the theory that a poor diet is primarily responsible for the increased metabolic syndrome risk seen in those with mental illness (39). Additionally, both the subjects with bipolar disorder and those with schizophrenia had a more favorable essential fatty acid N-6/N-3 ratio compared to NHANES subjects (Table 2). Elevations in this ratio are a potential cardiovascular disease risk factor (31, 40). While group differences were statistically significant between the NHANES subjects and subjects with schizophrenia, there was no statistically significant difference between NHANES subjects and subjects with bipolar disorder. Clinically, though, the impact of these differences is really unknown. Although both the subjects with bipolar disorder and those with schizophrenia are undoubtedly at greater metabolic syndrome risk due to the presence of mental illness, as well as other pharmacologic and non-pharmacologic risk factors, compared to NHANES controls, our study suggests that simply attributing this risk to diet does not appear to be sufficient.

In an effort to determine potential disease-specific differences that may be seen in dietary intake, we also examined differences between our matched subjects with bipolar disorder and schizophrenia, since recent literature has suggested similar metabolic syndrome risks (41, 42). Overall, the schizophrenia group had more cigarettes smokers, and they exercised less than the subjects with bipolar disorder (Table 3), yet the rate of metabolic syndrome was similar. Additionally, subjects with schizophrenia had lower total and LDL cholesterol levels compared to the bipolar disorder group. No diet intake differences were found between the two groups, which was not expected. For medications, the bipolar disorder group had higher mood stabilizer use, with no particular one being most common. Valproic acid has been associated with weight gain, but since only 25% of subjects with bipolar disorder were receiving valproate, its use cannot be significantly contributing to the metabolic differences we found. Similar rates of metabolic syndrome were seen for both of the age-, race-, and gender-matched groups, despite the fact that the bipolar disorder group, in general, participated in healthier lifestyle choices (exercise and

non-smoking) and had a lower incidence of AAP use. Additionally, although the subjects diagnosed with bipolar disorder had overall a similar percentage receiving AAPs (~80%), only half of the subjects with bipolar disorder were using an AAP with greater weight liability versus approximately three-fourths of the subjects with schizophrenia. Thus, the similarities in metabolic syndrome occurrence between the subjects with schizophrenia and bipolar disorder are troublesome given the fact that those diagnosed with bipolar disorder appeared to have overall lower risk factors related to diet, lifestyle, and medication. In general, polypharmacy is very common within the mental health disorder population, and this can also be seen in our study subjects, with antipsychotic use being seen in 50–70% of subjects, mood stabilizer use being seen in 30–70%, and antidepressant use being seen in 50–60%. While many individual agents have been associated with the occurrence of weight gain, the pathophysiology behind these associations varies depending on the agent being examined, but may be associated with the pharmacologic effect of medication on histamine, serotonin, and norepinephrine neurotransmission (43).

Lastly, we examined differences in dietary and lifestyle factors based upon metabolic syndrome criteria and found few differences. While most of the metabolic measures associated with metabolic syndrome (i.e., glucose, lipids, and BMI) were higher in those meeting NCEP-ATP-III criteria, no differences were found in AAP use, total chlorpromazine equivalents, mood stabilizer use, age, race, and gender. For dietary intake, no differences were found between the metabolic syndrome groups. Our regression model also mirrored this, but showed an interesting relationship between antidepressant use and metabolic syndrome, which remained significant after we controlled for age differences. Many antidepressants have been associated with weight loss and not weight gain, making this finding intriguing. The most commonly used antidepressants in our study group were bupropion and citalopram, which have different pharmacologic profiles. In general, bupropion has not been associated with significant weight gain, while citalopram may be associated with some weight gain with long-term use (44, 45). This then led us to hypothesize that antidepressant differences may be due to diagnostic distribution differences between the metabolic syndrome groups; however, no differences were found (Table 4). It could be that residual depressive symptoms and potential vegetative symptoms may be contributing to metabolic syndrome occurrence; however, this hypothesis is still very preliminary as we did not measure psychopathology as part of this study. While affective symptomatology within bipolar disorder is undoubtedly key, this has been less studied within schizophrenia, but is currently gaining interest (46). It is also important to point out the high percentage of patients in general who were receiving antidepressants as part of our investigation (~59%), as polypharmacy has also been implicated as a risk factor for metabolic syndrome (47). Additionally, long-standing research has shown a relationship between depression and cardiovascular disease (48). Thus, our reported relationship between antidepressant use and metabolic syndrome may be a surrogate marker for this known association. Regardless, for those patients with mental illness who require antidepressant use, thorough education regarding cardiovascular disease as well as metabolic monitoring is necessary when treatment is started. Although lifestyle and dietary habits are extremely important in maintaining cardiovascular health, we were unable to find significant dietary and/or lifestyle differences that predicted metabolic syndrome risk in subjects with bipolar disorder and schizophrenia.

Only one other study involving greater than 100 individuals has examined the dietary intake of individuals with schizophrenia (49). As part of this investigation, intake of antioxidants (vitamins A, C, and E) and fatty acids was estimated using a 24-hour diet recall similar to our investigation. However, in contrast to our study, these authors reported that subjects with schizophrenia had elevated saturated and polyunsaturated fatty acid intake, which was significant compared to the NHANES Cycle III results (50), and antioxidant intake was not significantly different between cases and controls. A smaller study examining 88 patients found that the BMI for individuals with schizophrenia was significantly higher than in controls. In addition, the schizophrenia group consumed significantly less carbohydrates, calories, total fat, saturated fat, monounsaturated fatty acids, polyunsaturated fatty acids, fiber, folate, alcohol, and sodium, and significantly more caffeine than the NHANES group (51). Thus, these data seem to agree with our current analysis.

The sole examination of the dietary intake of patients with bipolar disorder involved 23 women and found a significantly higher glycemic index compared to negative controls (52). In addition, their diet was generally classified as 'western', reflecting consumption of foods such as processed meats, pizza, chips, hamburgers, white bread, sugar, flavored milk drinks, and beer. This is very similar to our data showing an N-6/N-3 ratio

~10, indicating a more 'westernized' diet, in the bipolar and schizophrenia groups, as well as our metabolic syndrome groups (53). Most importantly, 40% of our study subjects met metabolic syndrome criteria before or during their early 40s, which is younger than reported in the general population, but in line with other reports (1). The bipolar disorder group, despite an overall healthier lifestyle, seemed to show a similar rate of metabolic syndrome compared to subjects with schizophrenia.

Limitations

While the results of this study are interesting, we need to be mindful of limitations. Our cross-sectional design does not allow for 'cause and effect' relationships. Additionally, we acknowledge that the persons administering the 24-hour food recount for our subjects were not the same individuals collecting these data as part of the NHANES study and that these differences in study personnel may introduce an unknown bias. While these limitations may be important to recognize for our analysis related to the NHANES subjects, for our secondary analysis between the matched subjects with bipolar disorder and schizophrenia the same registered dieticians used the same standardized procedures to collect the data, and thus these comparisons may be the most important to consider. Use of the NHANES data, while important, may not represent a timely indication of metabolic syndrome incidence within the general population since these data are from 1999 to 2000 and our data were collected from 2007 to 2011. Additionally, since we were unable to match subjects based on socioeconomic status or geographic region, the limitations associated with these potential differences also need to be acknowledged. This lack of matching is interesting because there are data suggesting that poorer dietary intake does correlate with socioeconomic status (54). Thus, if this were to hold true for this analysis, then we would expect an even greater difference between the patient groups compared to the NHANES data, as serious mental illnesses (specifically schizophrenia) have been associated with a lower socioeconomic status by some investigators, but not all (55–57). Arguably, subjects with a serious mental illness may be considerably different than subjects included in the NHANES database, and we need to recognize that the subjects with bipolar disorder and schizophrenia may be less able to recall dietary information. However, to overcome this potential limitation, we utilized three 24-hour food recounts and followed the same standardized NHANES procedures, carried out by experienced registered dieticians, in an effort to obtain accurate data related to usual dietary intake, without overburdening subjects with assessments. Lack of dietary blood levels hinders our ability to relate the body's handling of these nutrients in relation to metabolic syndrome. Lastly, while the sample size was relatively large for a mental health study, it would be considered rather small compared to studies within the general population and the results of this study need to be replicated.

Summary

In spite of the clear presence of higher rates of metabolic syndrome in both the bipolar and the schizophrenia groups, very few dietary differences could be discerned between the schizophrenia, bipolar disorder, and NHANES subject groups. Within the patient groups stratified by metabolic syndrome criteria and assessed by identical procedures, few differences in dietary and lifestyle practices could be discerned, suggesting that the lack of an association between metabolic syndrome and lifestyle factors is not an artifact of inaccurate recall of the patients. While these findings should not be taken to imply that dietary and lifestyle factors are not important in the development of metabolic syndrome in the general population, they do suggest that the mechanisms behind metabolic complications in individuals with serious mental illness are more complicated. It may be the case that the influence of pharmacologic agents on the development of these complications overrides lifestyle factors. If so, further research is warranted to design optimal interventions to combat these potentially life-threatening medication-related adverse events. Additional research specific to subjects diagnosed with bipolar disorder should also be undertaken to parse out the specific risk factors related to metabolic syndrome development, as our data suggest that, despite exhibiting 'healthier' lifestyle practices and lower AAP use, metabolic syndrome occurrence is elevated in these subjects.

Acknowledgements

Funding and support for the study was received from these sources: NIMH (R01 MH082784), NIH-NCCR, GCRC Program (UL1RR024986), the Chemistry Core of the Michigan Diabetes Research and Training Center (NIH5P60 DK 20572) (all Bethesda, MD, USA), the Washtenaw Community Health Organization (Ann Arbor, MI, USA), The Brain and Behavior Research Foundation (formerly NARSAD, Great Neck, NY, USA), and the Prechter Longitudinal Study of Bipolar Disorder (Ann Arbor, MI, USA).

Disclosures

The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

References

1. McEvoy JP, Meyer JM, Goff DC et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the clinical antipsychotic trials of intervention effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. Schizophr Res 2005; 80: 19–32.
2. McIntyre RS, Danilewitz M, Liauw SS et al. Bipolar disorder and metabolic syndrome: an international perspective. J Affect Disord 2010; 126: 366–387.
3. Davidson MH. A symposium: National Cholesterol Education Program Adult Treatment Panel III: impact and implementation of the new guidelines. Introduction. Am J Cardiol 2002; 89: 1C–2C.
4. Correll C, Frederickson A, Kane J, Manu P. Equally increased risk for metabolic syndrome in patients with bipolar disorder and schizophrenia treated with second-generation antipsychotics. Bipolar Disord 2008; 10: 788–797.
5. Ellingrod VL, Taylor SF, Dalack G et al. Risk factors associated with metabolic syndrome in bipolar and schizophrenia subjects treated with antipsychotics: the role of folate pharmacogenetics. J Clin Psychopharmacol 2012; 32: 261–265.
6. Ellingrod VL, Miller DD, Taylor SF, Moline J, Holman T, Kerr J. Metabolic syndrome and insulin resistance in schizophrenia patients receiving antipsychotics genotyped for the methylenetetrahydrofolate reductase (MTHFR) 677C/T and 1298A/C variants. Schizophr Res 2008; 98: 47–54.
7. van Winkel R, Rutten BP, Peerbooms O, Peuskens J, van Os J, De Hert M. MTHFR and risk of metabolic syndrome in patients with schizophrenia. Schizophr Res 2010; 121: 193–198.
8. Belin R, Greenland P, Allison M et al. Diet quality and the risk of cardiovascular disease: the Women's Health Initiative (WHI). Am J Clin Nutr 2011; 94: 49–57.
9. Bowles D, Laughlin MH. Mechanism of beneficial effects of physical activity on atherosclerosis and coronary heart disease. J Appl Physiol 2011; 111: 308–310.
10. Dubbert P, Carithers T, Sumner A et al. Obesity, physical inactivity, and risk for cardiovascular disease. Am J Med Sci 2002; 324: 116–126.
11. Gade W, Schmit J, Collins M, Gade J. Beyond obesity: the diagnosis and pathophysiology of metabolic syndrome. Clin Lab Sci 2010; 23: 61.
12. Colton C, Manderscheid R. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. Prev Chronic Dis 2006; 3: A42.
13. Leao LS, de Moraes MM, de Carvalho GX, Koifman RJ. Nutritional interventions in metabolic syndrome: a systematic review. Arq Bras Cardiol 2011; 97: 260–265.
14. Ellingrod V, Taylor S, Brook R et al. Dietary, lifestyle and pharmacogenetic factors associated with arteriole endothelial-dependent vasodilatation in schizophrenia patients treated with atypical antipsychotics (AAPs). Schizophr Res 2011; 130: 20–26.
15. Langenecker SA, Saunders EF, Kade AM, Ransom MT, McInnis MG. Intermediate: cognitive phenotypes in bipolar disorder. J Affect Disord 2010; 122: 285–293.
16. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 1999-2000. Available from: http://www.cdc.gov/nchs/nhanes [accessed November 2011].
17. Spitzer RL, Williams JB, Gibbon M, First MB. The structured clinical interview for DSM-III-R (SCID). I: history, rationale, and description. Arch Gen Psychiatry 1992; 49: 624–629.
18. Nurnberger JI Jr, Blehar MC, Kaufmann CA et al. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. Arch Gen Psychiatry 1994; 51: 849–859.
19. Andreasen NC, Pressler M, Nopoulos P, Miller D, Ho BC. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. Biol Psychiatry 2010; 67: 255–262.
20. Rummel-Kluge C, Komossa K, Schwarz S et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. Schizophr Res 2010; 123: 225–233.
21. Moshfegh AJ, Rhodes DG, Baer DJ et al. The US department of agriculture automated multiple-pass method reduces bias in the collection of energy intakes. Am J Clin Nutr 2008; 88: 324–332.
22. Schatzkin A, Kipnis V, Carroll RJ et al. A comparison of a food frequency questionnaire with a 24-hour recall for use in an epidemiological cohort study: results from the biomarker-based observing protein and energy nutrition (OPEN) study. Int J Epidemiol 2003; 32: 1054–1062.
23. Kipnis V, Subar AF, Midthune D et al. Structure of dietary measurement error: results of the OPEN biomarker study. Am J Epidemiol 2003; 158: 14–21.
24. Subar AF, Kirkpatrick SI, Mittl B et al. The Automated Self-Administered 24-hour dietary recall (ASA24): a resource for researchers, clinicians, and educators from the National Cancer Institute. J Acad Nutr Diet 2012; 112: 1134–1137.
25. Dipasquale S, Pariante CM, Dazzan P, Aguglia E, McGuire P, Mondelli V. The dietary pattern of patients with schizophrenia: a systematic review. J Psychiatr Res 2013; 47: 197–207.
26. Schakel SF. Maintaining a nutrient database in a changing marketplace: keeping pace with changing food products – a research perspective. J Food Composit Anal 2001; 14: 315–322.
27. Orrell A, Doherty P, Miles J, Lewin R. Development and validation of a very brief questionnaire measure of physical activity in adults with coronary heart disease. Eur J Cardiovasc Prev Rehabil 2007; 14: 615–623.
28. Simopoulos AP. Evolutionary aspects of diet: the omega-6/omega-3 ratio and the brain. Mol Neurobiol 2011; 44: 203–215.
29. Komossa K, Rummel-Kluge C, Hunger H et al. Ziprasidone versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev 2009; 4: CD006627.
30. Marik P, Varon J. Omega-3 dietary supplements and the risk of cardiovascular events: a systematic review. Clin Cardiol 2009; 32: 365–372.

31. Burghardt PR, Kemmerer ES, Buck BJ et al. Dietary n-3: N-6 fatty acid ratios differentially influence hormonal signature in a rodent model of metabolic syndrome relative to healthy controls. Nutr Metab 2010; 7: 53.
32. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the Third National Health and Nutrition Examination Survey. JAMA 2002; 287: 356–359.
33. Meyer JM, Nasrallah HA, McEvoy JP et al. The clinical antipsychotic trials of intervention effectiveness (CATIE) schizophrenia trial: clinical comparison of subgroups with and without the metabolic syndrome. Schizophr Res 2005; 80: 9–18.
34. Goff DC, Sullivan LM, McEvoy JP et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. Schizophr Res 2005; 80: 45–53.
35. Daumit GL, Goff DC, Meyer JM et al. Antipsychotic effects on estimated 10-year coronary heart disease risk in the CATIE schizophrenia study. Schizophr Res 2008; 105: 175–187.
36. Patel JK, Buckley PF, Woolson S et al. Metabolic profiles of second-generation antipsychotics in early psychosis: findings from the CAFE study. Schizophr Res 2009; 111: 9–16.
37. Vik-Mo AO, Birkenaes AB, Ferno J, Jonsdottir H, Andreassen OA, Steen VM. Increased expression of lipid biosynthesis genes in peripheral blood cells of olanzapine-treated patients. Int J Neuropsychopharmacol 2008; 11: 679–684.
38. Popkin BM, Adair LS, Ng SW. Global nutrition transition and the pandemic of obesity in developing countries. Nutr Rev 2012; 70: 3–21.
39. Megna JL, Schwartz TL, Siddiqui UA, Herrera Rojas M. Obesity in adults with serious and persistent mental illness: a review of postulated mechanisms and current interventions. Ann Clin Psychiatry 2011; 23: 131–140.
40. Wall R, Ross RP, Fitzgerald G, Stanton C. Fatty acids from fish: the anti-inflammatory potential of long-chain omega-3 fatty acids. Nutr Rev 2010; 68: 280–289.
41. Correll CU, Lencz T, Malhotra AK. Antipsychotic drugs and obesity. Trends Mol Med 2011; 17: 97–107.
42. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol 2011; 8: 114–126.
43. McIntyre RS, Park KY, Law CW et al. The association between conventional antidepressants and the metabolic syndrome: a review of the evidence and clinical implications. CNS Drugs 2010; 24: 741–753.
44. Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. J Clin Psychiatry 2010; 71: 1259–1272.
45. Uher R, Mors O, Hauser J et al. Changes in body weight during pharmacological treatment of depression. Int J Neuropsychopharmacol 2011; 14: 367–375.
46. Taylor SF, Kang J, Brege IS, Tso IF, Hosanagar A, Johnson TD. Meta-analysis of functional neuroimaging studies of emotion perception and experience in schizophrenia. Biol Psychiatry 2012; 71: 136–145.
47. Misawa F, Shimizu K, Fujii Y et al. Is antipsychotic polypharmacy associated with metabolic syndrome even after adjustment for lifestyle effects? A cross-sectional study. BMC Psychiatry 2011; 11: 118.
48. Elderon L, Whooley MA. Depression and cardiovascular disease. Prog Cardiovasc Dis 2013; 55: 511–523.
49. Strassnig M, Singh Brar J, Ganguli R. Dietary fatty acid and antioxidant intake in community-dwelling patients suffering from schizophrenia. Schizophr Res 2005; 76: 343–351.
50. Alaimo K, McDowell MA, Briefel RR et al. Dietary intake of vitamins, minerals, and fiber of persons ages 2 months and over in the United States: Third National Health and Nutrition Examination Survey, Phase 1, 1988-91. Adv Data 1994; 258: 1–28.
51. Henderson DC, Borba CP, Daley TB et al. Dietary intake profile of patients with schizophrenia. Ann Clin Psychiatry 2006; 18: 99–105.
52. Jacka FN, Pasco JA, Mykletun A et al. Diet quality in bipolar disorder in a population-based sample of women. J Affect Disord 2011; 129: 332–337.
53. Wertz PW. Essential fatty acids and dietary stress. Toxicol Ind Health 2009; 25: 279–283.
54. Gordon-Larsen P, Popkin B. Understanding socioeconomic and racial/ethnic status disparities in diet, exercise, and weight: underlying contextual factors and pathways. J Am Diet Assoc 2011; 111: 1816–1819.
55. Isaac M, Chand P, Murthy P. Schizophrenia outcome measures in the wider international community. Br J Psychiatry Suppl 2007; 50: S71–S77.
56. McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev 2008; 30: 67–76.
57. McGrath J, Saha S, Welham J, El Saadi O, MacCauley C, Chant D. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. BMC Med 2004; 2: 13.