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Metabolic Syndrome In Bipolar Disorder and Schizophrenia: Dietary and Lifestyle Factors Compared to the General Population

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Abstract

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 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 bipolar (33%) and schizophrenia (47%) samples compared to matched NHANES controls (17% and 11%, respectively), and not different between the patient groups. Surprisingly, both bipolar disorder and schizophrenia subjects consumed fewer total calories, carbohydrates and fats, as well as more fiber

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($p < 0.03$), compared to NHANES controls. No dietary or activity differences between patient participants with and without metabolic syndrome were found. Schizophrenia subjects had significantly lower total and low density cholesterol levels ($p < 0.0001$) compared to NHANES controls. Bipolar disorder subjects smoked less ($p = 0.001$), exercised more ($p = 0.004$), and had lower BMIs ($p = 0.009$) compared to schizophrenia subjects.

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

Keywords

Schizophrenia; Bipolar Disorder; Dietary Intake; Atypical Antipsychotics; Metabolic Syndrome

Introduction

The relationships between cardiovascular disease and medication use for those diagnosed with bipolar and schizophrenia are gaining increasing attention. In looking at our previous work as well as other reports in the literature, approximately 40% of those with a serious mental illness meet 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, 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 and schizophrenia compared to 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 bipolar and schizophrenia subjects in regards to dietary intake (both general dietary and 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 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

Bipolar and schizophrenia Study Subjects

Subjects in this analysis met the following inclusion criteria: 1) DSM-IV diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, or bipolar disorder I or II, 2) ≥18 years old, and 3) pharmacologic mental health treatment for at least 6 months. Subjects were excluded if they 1) were unable to provide informed consent (assessed using a short questionnaire asking key questions about the study), 2) had documented type II diabetes before antipsychotic treatment started, or 3) 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 critiera 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 from 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 3 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 to the NHANES subjects with the matched bipolar and schizophrenia subjects. We were unable to match the bipolar and schizophrenia subjects with the NHANES controls in regards to education, years of employment, living situation or socioeconomic status.

Assessments

Bipolar and schizophrenia subjects meeting inclusion and exclusion criteria underwent informed consent including a brief assessment of the risks and benefits associated with study participation. Afterwards, a clinical interview, which included the Structured Clinical Interview for DSM Diagnoses (SCID) for schizophrenia patients (17), or the Diagnostic Interview for Genetic Studies (DIGS) for the bipolar disorder subjects (18) was completed by a trained research assistant, to confirm the psychiatric diagnosis. Different diagnostic instruments were used as 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 (>8 hours) before the study visits which took place between 8am and noon, or within 2 hours of their usually waking time based on appointment availability. Vital signs (i.e. height, weight), and hip and waist circumference 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 last 24 hours prior to fasting**,** which 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 last 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, was then used to calculate average calorie intake using the Nutrition Data Systems for Research software (NDSR) developed by the Nutrition Coordinating Center (NCC) at the University of Minnesota (26). The output from these analyses was averaged over the 2 recalls for the NHANES controls and 3 recalls for the bipolar and schizophrenia subjects. 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), omega 6 fatty acids (N-6), the N-3/N-6 ratio, total fat and saturated fatty acid (SFAs), and poly unsaturated 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 bipolar and schizophrenia subjects consisted of questions about smoking (number of cigarettes smoked per day, age at 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 at MET/minute. Data related to these lifestyle assessments was not available for the NHANES controls.

Blood was obtained from fasting bipolar and schizophrenia subjects for the following assessments: glucose, insulin, hemoglobin A1c, 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 3 of the following: 1) abdominal obesity characterized by waist circumference of >40 inches for men or >35 inches for women, 2) triglycerides ≥150 mg/dL, 3) HDL cholesterol <40 mg/dL for men and <50 mg/dL for women or receiving a lipid lowering agent), 4) blood pressure ≥130/≥85 mmHg or treatment for hypertension, or 5) 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 versions 8 or 9 (SAS Institute, Cary, NC). For our primary aim, we examined differences between the bipolar and schizophrenia subjects compared to race, gender, and age (within 3 years) NHANES subjects. For our second analysis, we were interested in determining differences between the bipolar and schizophrenia subject groups, thus subjects within these two groups were also matched by race, gender, and age (within 3 years) resulting in a smaller subset of these patients being included in this analysis.

Differences for the primarily outcomes and socio-demographic 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, and 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 earlier 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 our tables and discussed below. A general linear regression was done to determine dietary and lifestyle predictors of metabolic syndrome using metabolic syndrome (and its individual components) as the dependent variables, and age, race, gender, atypical antipsychotic (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 for Subjects Diagnosed with Bipolar Disorder, Schizophrenia and NHANES Controls

A total of 143 subjects with schizophrenia, 116 subjects with bipolar disorder, and 259 age (within 3 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 meet criteria for metabolic syndrome; the difference was not statistically different ($p = 0.52$). These rates are significantly higher than what was seen in the NHANES controls (11% and 17%) 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 general population (cholesterol and low density lipoproteins (169 mg/dl vs 196 md/dl, $p < 0.0001$), while no differences were found for the bipolar disorder group (191 mg/dl vs 188 mg/dl, $p= 0.51$) when they were compared to NHANES subjects.

Dietary differences between the groups and the NHANES subjects are detailed in Table 2. In general, both the bipolar 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 ($p = 0.048$) as well as monounsaturated fatty acids ($p = 0.03$). No other differences were found in the average dietary intake for either the bipolar disorder or schizophrenia groups 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 the schizophrenia subjects ($p= 0.02$), although for all 4 groups, this ratio was around 10 which is above the recommended intake ratio of 1 to 4 (28).

Differences Between Matched Bipolar and schizophrenia Subjects

In order to determine disease specific differences in diet and lifestyle factors that may affect metabolic syndrome occurrence, a subset of our bipolar and schizophrenia subjects were also matched by race, gender, and age (within 3 years) resulting in a 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 age of this group was 45.1 ± 10.9 years, and were 60% female, 80% Caucasian and 13% African American. A description of demographic, dietary, lifestyle and metabolic differences between bipolar and schizophrenia patients 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 cholesterol measurements (194 mg/dl vs 174 mg/dl, $p = 0.009$) and low density lipoproteins (120.3 mg/dl vs 102.7 mg/dl, $p = 0.005$) compared to schizophrenia subjects. We had hypothesized that this might be due to 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 statistical 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 amongst the bipolar 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 equivalents ($p= 0.0002$), 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 medication 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 bipolar disorder subjects and 84% of the schizophrenia subjects were receiving AAPs which was not statistically different ($p = 0.22$). We also examined use of other psychotropic medications between each group and found more mood stabilizer usage within the bipolar disorder group (79% vs 30%, $p < 0.0001$); however no differences were seen in regards to antidepressant, antihypertensive, oral hypoglycemic, and lipid lowering agents usage ($p> 0.2$ 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 amongst these groups. Most notably, mean omega 3 fatty acids (n-3) intake was 1.8 grams/day, which is within the recommended consumption of 1-2 grams/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 ratio around 1-4 for optimal cardiovascular health (31). In terms of other lifestyle differences, the bipolar disorder population displayed healthier choices in that fewer of them smoked cigarettes (45% versus 70%, $p = 0.001$) and they reported more physical activity ($p= 0.004$). Thus, despite participating in overall healthier lifestyle choices, having healthier diets, and lower AAP use compared to the schizophrenia subjects, those with bipolar disorder still were at an increased risk for metabolic syndrome.

Metabolic Syndrome Differences

For this analysis, the age, race, and gender matched bipolar and schizophrenia subjects previously discussed were stratified by metabolic syndrome criteria (32). Group differences are outlined in Table 4. Those with metabolic syndrome were slightly older (48 vs 43 years old, $p=0.004$), with no differences in race, gender or percent that smoked cigarettes. Additionally within both groups, approximately 60% reported AAP use (68% versus 57%, $p = 0.17$), however antidepressant use was higher in the metabolic syndrome group (69% versus 49%, $p = 0.01$). In looking at the pre-determined dietary variables of interest, no differences were found. Thus, despite meeting criteria for metabolic syndrome, the diet and

lifestyle choices of those classified as meeting metabolic syndrome looks very similar to those 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%CI: 1.33 - 14.9).

Discussion

Overall, our study found metabolic differences between bipolar and schizophrenia patients and NHANES, which was not surprising given extensive previous work (1, 33-36). Contrary to expectations, the bipolar and schizophrenia subject groups 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. Schizophrenia subjects showed lower cholesterol and low density lipoproteins levels, compared to NHANES, 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 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 piven that a poor diet, is primarily responsible for the increased metabolic syndrome risk seen in those with mental illness, (39). Additionally both the bipolar and schizophrenia subjects 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 and schizophrenia subjects, there was no statistical difference between NHANES and bipolar subjects. Clinically though, the impact of these differences is really unknown. Although both the bipolar and schizophrenia subjects are undoubtedly at greater metabolic syndrome risk due to the presence of mental illness, as well as other pharmacologic and non-pharmacologic risk factors, use, 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 bipolar and schizophrenia subjects 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 bipolar disorder subjects (Table 3), yet the rate of metabolic syndrome was similar. Additionally schizophrenia subjects had lower cholesterol and low density lipid 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 bipolar disorder subjects 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 bipolar subjects were using an AAP with greater weight liability versus approximately three-fourths of the schizophrenia subjects. Thus, the similarities in metabolic syndrome occurrence between the schizophrenia and bipolar subjects are troublesome given the fact that those diagnosed with bipolar disorder appear to have overall lower risk factors related to dietary, lifestyle, and medication factors. In general, polypharmacy is very common within the mental health 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 examine 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 both 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 lead 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 that 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 associated. Regardless, for those patients with mental illness who require antidepressant use, thorough education regarding cardiovascular disease as well a 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 with bipolar disorder and schizophrenia subjects.

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 were estimated using a 24-hour diet recall similar to our investigation. However, in contrast to our study, these authors reported that schizophrenia subjects 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 fewer 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, this data seems to agree with our current analysis.

The sole examination of the dietary intake of bipolar disorder patients has 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 within their early forties, which is younger than that 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 schizophrenia subjects.

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 this 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 bipolar and schizophrenia subjects 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 this data is from 1999-2000 and our data were collected from 2007-2011. Additionally since we were unable to match subjects based on socioeconomic status or geographic region the limitations associated with these potential differences also needs to be acknowledged. This lack of matching is interesting because there is 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 bipolar and schizophrenia subjects 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 get accurate data related to usual dietary intake, without overburdening subjects with assessments. Lack of dietary blood levels hinder our ability to relate the body's handling of these nutrients in relation 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 bipolar and 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.

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Table 1

Differences in laboratory and dietary measures between age, race, and gender matched schizophrenia, bipolar disorder, and general population controls.

Measurement (s.d)	**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 B.P. (mm Hg)	124.6 (17.1)	122.3 (21.3)	0.0052
Diastolic B.P. (mm Hg)	75.9 (12.7)	70.8 (14.3)	0.0012
Homocysteine (umol/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 (6.23)	3.25 (2.75)	<0.0001
Measurement (s.d)	**Bipolar Disorder**	**NHANES Matches**	**P-value**
	(n = 116)	**(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 B.P. (mm Hg)	123.6 (18.1)	116.6 (16.7)	0.58
Diastolic B.P. (mm Hg)	73.0 (10.9)	69.9 (13.0)	0.07
Homocysteine (umol/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	8.15 (13.09)	3.36 (3.09)	<0.0001

Table 2

Dietary and Lifestyle variables between groups Comparison of dietary intake and lifestyle measures between age, race, and gender matched schizophrenia, bipolar disorder, and NHANES patients.

Measurement (s.d.)	**Schizophrenia (n = 143)**	**NHANES (n = 143)**	**P-value**
Energy Consumed (kcal/day)	2072 (736)	2291 (1084)	0.031
Carbohydrates (Consumed) (g/day)	260.9 (100.6)	294.0 (151.7)	0.037
Saturated Fatty Acids Consumed (g/day)	28.3 (11.8)	28.5 (17.8)	0.89
Fiber Consumed (g/day)	17.2 (9.0)	12.2 (8.8)	<0.0001
Fat Consumed (g/day)	81.4 (33.1)	85.4 (49.0)	0.39
Poly unsaturated Fatty Acids Consumed (g/day)	17.1(9.4)	17.8(11.6)	0.57
Protein Consumed (g/day)	79.0 (32.9)	82.0 (43.4)	0.47
Mono unsaturated Fatty Acids Consumed (g/day)	29.3 (12.7)	32.6 (19.6)	0.08
Omega-3 Fatty Acids Consumed (g/day)	1.66 (0.88)	1.65 (1.27)	0.94
Omega-6 Fatty Acids Consumed (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 (s.d.)	**Bipolar Disorder (n = 116)**	**NHANES (n = 116)**	**P-value**
Energy Consumed (kcal/day)	1896 (609)	2309 (1021)	0.0005
Carbohydrates (Consumed) (g/day)	241.0 (92.2)	300.5 (172.6)	0.0007
Saturated Fatty Acids Consumed (g/day)	24.4 (11.9)	29.6 (16.2)	0.0073
Fiber Consumed (g/day)	19.0 (10.2)	14.7 (9.7)	0.0007
Fat Consumed (g/day)	74.3 (31.2)	84.7 (41.3)	0.048
Poly unsaturated Fatty Acids Consumed (g/day)	16.6 (7.5)	16.7 (9.9)	0.96
Protein Consumed (g/day)	73.3 (22.9)	82.3 (38.8)	0.056
Mono unsaturated Fatty Acids Consumed (g/day)	27.3 (12.8)	31.8 (16.6)	0.030
Omega-3 Fatty Acids Consumed (g/day)	1.80 (0.92)	1.61 (1.05)	0.16
Omega-6 Fatty Acids Consumed (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

Table 3

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

Variable	Schizophrenia (N=78)	Bipolar Disorder (N=78)	p-value
Demographics			
Age ± s.d. (years)	45.1 ± 10.9	46.1 ± 10.9	0.59
Percent Caucasian/African American	77%/17%	84%/12%	0.29
Percent Male	40	40	1
Using Atypical Antipsychotics	74	53	0.009
Metabolic Parameters			
Body Mass Index (BMI) ± s.d. (kg/m2)	34.1 ± 8.7	32.1 ± 7.7	0.13
Hip/Waist Ratio	1.05 ± 0.09	1.09 ± 0.11	0.02
Systolic Blood Pressure ± s.d. (mmHg)	122 ± 18	124 ± 19	0.63
Diastolic Blood Pressure ± s.d. (mmHg)	74 ± 12	74 ± 11	0.98
Homocysteine ± s.d. (umol/L)	11.3 ± 6.0	10.8 ± 3.4	0.64
Total Cholesterol ± s.d. (mg/dl)	173.9 ± 46.2	194.5 ± 49.3	0.009
High Density Lipoprotein ± s.d. (mg/dl)	54.5 ± 17.5	56.7 ± 16.0	0.43
Low Density Lipoproteins ± s.d. (mg/dl)	102.7 ± 33.4	120.3 ± 41.8	0.005
Triglycerides ± s.d. (mg/dl)	134.9 ± 101.7	160.2 ± 111.3	0.15
Glucose ± s.d. (mg/dL)	107.2 ± 46.6	104.4 ± 36.7	0.67
Meeting ATP-III Metabolic Syndrome Criteria (%)	42%	37%	0.52
HOMA-IR ± s.d.	6.7 ± 6.9	8.7 ± 16.1	0.35
Dietary and Lifestyle Parameters			
Current Smoker (%)	70	45	0.001
Total Activity Score (TAM2) ± s.d. MET/min	2423 ± 2492	4027 ± 4096	0.004
Mean Total Kcals consumed/day ± s.d. (Kcals/day)	1990±735	1953±656	0.74
Mean Carbohydrates consumed ± s.d. (kcals/day)	250±100	246 ± 96	0.82
Mean Total Fat consumed ± s.d. (grams/day)	79 ± 35	77 ± 34	0.71
Mean Poly Unsaturated Fats (PUFAs) consumed ± s.d. (grams/day)	17 ± 10	17 ± 8	0.96
Mean Saturated Fatty Acids (SFAs) consumed ± s.d. (grams/day)	29 ± 12	26 ± 13	0.30
Mean Dietary Fiber Consumed ± s.d. (grams/day)	18 ± 10	18 ± 9	0.71

Variable	Schizophrenia (N=78)	Bipolar Disorder (N=78)	p-value
Glycemic Index (Glucose Reference)	59.4 ± 4.9	60.2 ± 7.4	0.39
Mean Omega-3 Fatty Acids consumed ± s.d (grams/day)	1.9 ± 0.9	1.8 ± 1.0	0.16
Mean Omega-6 Fatty Acids consumed ± s.d (grams/day)	16.6 ± 9.7	16.6 ± 7.9	0.98
Mean Omega-6/Omega-3	11.1 ± 4.3	10.1 ± 4.7	0.17
Medications			
Mean Cumulative Chlorpromazine Equivalents (mg)	439.7 ± 326.8	247.4 ± 308.2	0.0002
Current receiving a mood stabilizer (%)	30%	79%	<0.0001
Currently receiving an antidepressant (%)	54%	60%	0.42
Currently receiving an antihypertensive (%)	31%	28%	0.73
Currently receiving a lipid lowering medication (%)	29%	22%	0.27
Currently receiving an oral hypoglycemic medication (%)	15%	6%	0.22

Table 4

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

Variable	With Metabolic Syndrome (n = 62)	Without Metabolic Syndrome (n = 94)	p-value
Demographics			
Age ± s.d. (years)	48.7 ± 9.7	43.5 ± 11.1	0.004
Percent Caucasian/African American	83%/12%	79%/16%	0.92
Percent Male	60%	60%	0.90
% Schizophrenia/ % Bipolar	47%/53%	52%/47%	0.51
AAP use (%)	68%	57%	0.17
Mean Cumulative Chlorpromazine Equivalents (mg)	438.7 ± 439.0	401.9 ± 379.1	0.58
Current receiving a mood stabilizer (%)	55%	55%	0.95
Currently receiving an antidepressant (%)	69%	49%	0.01
Dietary and Lifestyle Parameters			
Percent Current Smoker	53%	41%	0.15
Mean Total Calories consumed/day ± s.d. (Kcals)	1973.9 ± 657.6	1973.2 ± 737.5	0.96
Total Activity Score (TAM2) ± s.d. MET/min	2902 ± 2797	3738 ± 3856	0.35
Mean Carbohydrates consumed ± s.d. (kcals/day)	245.2 ± 92.9	251.0 ± 101.1	0.72
Mean Saturated Fatty Acids (SFAs) consumed ± s.d. (grams/day)	27.5 ± 13.5	26.5 ± 12.6	0.63
Mean Dietary Fiber consumed ± s.d. (grams/day)	17.8 ± 8.9	18.2 ± 9.5	0.83
Mean Total Fat consumed ± s.d. (grams/day)	79.9 ± 34.8	77.7 ± 34.5	0.69
Mean Poly unsaturated Fats (PUFAs) consumed ± s.d. (grams/day)	16.6 ± 9.1	16.9 ± 8.7	0.85
Mean Vitamin D consumed ± s.d. (micrograms/day)	7.7 ± 7.7	7.4 ± 12.7	0.87
Glycemic Index (Glucose Reference)	59.7 ± 4.8	59.8 ± 7.1	0.93
Mean Omega-3 Fatty Acids consumed ± s.d (grams/day)	1.6 ± 0.9	1.8 ± 1.0	0.38
Mean Omega-6 Fatty Acids consumed ± s.d (grams/day)	16.3 ± 8.9	16.7 ± 8.7	0.80
Mean Omega-6/Omega-3	11.0 ± 4.4	10.4 ± 4.6	0.64