

We have responded point by point to reviewer comments and included relevant additions to manuscript with new or changed sections underlined.

Reviewer code: 02445242

The manuscript does not seem to have an abstract or a 'core tip'. INTRODUCTION There is no mention of obesity in the 'purpose of the study'. METHODS Could the authors mention the procedure used to screen patients for diabetes? RESULTS Since the presence of diabetes was obtained via self-report, primary care records and screening it would be useful to know the number of patients with a positive diagnosis in each category. DISCUSSION A few line on the advantages & disadvantages of the BMI as a sole index of obesity could be added

We have resubmitted the abstract and core tip with revised paper.

Obesity is added to diabetes in describing the purpose of the paper.

We have made clearer the description of methods to indicate that both self-report and verification of primary care records was used to document diagnosis of diabetes. New diagnosis was by lab testing (HbA1c).

We have clarified that all self-reported diabetes diagnosis was subsequently verified by primary care records. The diabetes diagnosis in this retrospective study was primarily through self-report/primary care records.

We included a discussion on why BMI was used as an index of obesity in the methods section. We have also added a relevant reference for this.

“While waist circumference is a better indicator of abdominal obesity and subsequent cardiovascular risk, it is not clear that it offers additional information for clinical management. Also it is not part of usual care due to provider discomfort[12]. Hence, BMI was used as an index for obesity in this study. Diabetes mellitus (DM) type 2 diagnosis was extracted from the chart by self-report and verified by obtaining primary care records. In addition, patients were screened at least yearly for diabetes by glycosylated hemoglobin (HbA1c) and referred for treatment if they tested positive”.

Reviewer code: 00058872

Nice research. Authors are kindly requested to take into serious consideration that an increase of the OR from 2.4 to 3.5 in predicting diabetes, when schizophrenia is adjusted for obesity, thus of nearly 46%, is indicative that this specific variable is a real confounding factor of not scarce weight. The role of IL-6 (common factor present in schizophrenia and obesity) in inducing IR should be further emphasised. Physical activity could be another key factor. What about NAFLD presence?

We have restructured the sentence in the discussion section describing the risk of diabetes after controlling for obesity in schizophrenia. We make it clear that obesity does have a role though does not account for all the diabetes risk. We have also added a few lines in the discussion section emphasizing the role of inflammatory cytokines and physical activity in development of insulin resistance.

“But a notable finding is that after controlling for BMI and obesity status, the risk of diabetes remained significant, though lower”.

“Many other factors including an innate risk may be responsible for the higher prevalence of obesity and diabetes in the schizophrenia population. An inherent susceptibility to diabetes in schizophrenia patients is supported by studies with medication naive first episode psychosis patients [10]. The inherent risk for diabetes may be mediated in part by elevated levels of inflammatory cytokines seen in both schizophrenia and obesity[9]”

“An innate predisposition to diabetes, seen in first episode psychosis patients, may be compounded by antipsychotic medications, lower socioeconomic status and decreased access to quality health care. Patients with schizophrenia also are less physically active contributing further to insulin resistance”.

Reviewer code: 00058696

This manuscript has been carefully examined. My major questions are: 1) What is the authors' hypothesis? 2) How is the authors' patient population distinct from prior published studies? 3) Diagnosis of diabetes mellitus by "self-report" is not accurate. There are published definitions for a diagnosis of diabetes mellitus. 4) The authors use 3 separate phrases: population data, population control, and control group. Are these all the same? 5) The "Control Group" is NOT similar to the disease group. The results are not reliable. 6) Table 1 cannot stand alone. No p values are included in Table 1. 7) Figures 1, 2, and 3 are unreliable because the disease group and population control are not similar

The aim was to evaluate if the higher prevalence of obesity and diabetes seen in schizophrenia patients was seen when a patient sample was compared to controls in the same geographic area. We have also now added a hypothesis.

One of the strengths of our study is that our patient population is a naturalistic sampling of community dwelling people with schizophrenia. They were not recruited specifically for purposes of the study. We have mentioned this strength in the discussion section.

We agree that diabetes has very specific definitions for diagnosis. However, as per the United States Centers for Disease Control national survey, self-report of diabetes correlates with diagnosis by lab testing.

We have now changed terminology to consistently use 'control group' in all sections to refer to the population control sample.

We agree that the control group is not similar to the disease group. This is because this is not a controlled study, rather it is a naturalistic sampling. The naturalistic sampling allows for applicability of results to real world settings. The two groups belong to the same geographic community. Also, we control for demographic variables when presenting risk of obesity and diabetes in people with schizophrenia.

We have now added p values in table 1.

Yes, we agree figures represent comparison of disease and population groups with different demographics. However, when controlled for these variables, the differences between the two groups still remain significant.

“The purpose of this study is to compare the prevalence of obesity and diabetes in patients with schizophrenia treated at a community mental health center with population controls in the same metropolitan area. The authors hypothesized that the prevalence would be higher in patients with schizophrenia”.

“Strengths of this study include the large naturalistic sampling of community dwelling schizophrenia patients as well as a local population control sample in the same geographic area. Patients were not recruited for the study, instead all patients in the Psychosis Program with diagnosis of schizophrenia were included. This study design allows for applicability of results to real world settings. In the community mental health center sample, schizophrenia diagnosis was based on a structured interview and diabetes diagnosis was established based on previous lab diagnosis. A limitation is that the BRFSS survey data was based on self-report. Also the antipsychotic use is cross sectional and results may be confounded by changes in the type of antipsychotic used throughout patients’ disease history. Since this was not a controlled study, demographic variables were different between the disease and control groups. While these may confound results, in our study, higher prevalence of obesity and diabetes in schizophrenia persisted after controlling for these variables”.

Reviewer code: 02955074

The manuscript is well written and concise. The limitations of the study are restricted population demographics. The authors should have compared their study with other published reports from areas around New Haven. Certain laboratory tests with the study would have been supportive information.

We agree that it would have been helpful to compare our results with other published reports in the area rather than with local population. However, there are no other published reports from New Haven. We agree that lab tests would have yielded useful information, however, we did not have access to that information in this chart review.

Reviewer code: 00504962

The authors examined prevalence of obesity and diabetes in patients with schizophrenia. The purpose of this study is to compare the prevalence of diabetes in patients with schizophrenia treated at a community mental health center with matched controls in the same metropolitan area. The study also examines the effect of antipsychotic exposure on diabetes prevalence in schizophrenia patients. It is very important topic in the field.

1. Several studies also demonstrated the relation of obesity, glucose intolerance and diabetes in patients with schizophrenia. Authors should clearly describe the novel point in the present study. 2. The population group had a higher percentage of overweight subjects and schizophrenia group had a higher percentage of obesity. In addition, antipsychotic medication dosage was not significantly correlated with BMI either in the entire group or the obese group. It would be better to discuss the point in greater detail. Please add ABSTRACT of the manuscript and a standard error in the Figures.

We have now emphasized in our discussion section the uniqueness of using a naturalistic sample of schizophrenia patients and local population control from the same community. See our response above to Reviewer code: 00058696.

We have emphasized in our discussion the significance of lack of differential effects of antipsychotics on obesity categories.

We have resubmitted an abstract with the revised paper.

We have included error bars in the figures.

“It is notable that antipsychotic medication factors did not account for the differences in either obesity or diabetes status within the schizophrenia group. Neither the antipsychotic category nor the medication dose correlated with obesity”.

Reviewer by email:

My comments would include that the control group is very dissimilar from the study group: they are not attending a MD visit, they are older, they are a national group while the study group is local to Connecticut, and there are fewer males and less African Americans. At the very least, these differences need to be pointed out and discussed. Somewhere in the manuscript, I recommend to at least mention that the focus is on type 2 diabetes.

Many times in the manuscript there is a reference to $p < 0.000$. There is no such thing as a p value less than zero!

We have added a few lines in the discussion on the limitations of using a population control which resulted in different demographics. See also response to Reviewer code: 00058696.

We have changed the representation of the p value in the entire document.