Author’s response to reviews

Title: The prevalence of metabolic syndrome in patients receiving antipsychotics in Qatar: A cross sectional comparative study

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The following are the point-to-point responses (in italics) to the reviewers’ comments (in bold). Corresponding changes in the manuscript are underlined in the new version.
Reviewer 1:

The authors are congratulated on a very well written and well organised manuscript. The Abstract and Introduction are well laid out, concise and informative. The review of extant literature is comprehensive, appropriate, and informed the scope and aim of the study. The aim for the study and hypothesis are well articulated. Sample sizes were determined based on appropriate statistical rationale. As a minor comment, the exclusionary criteria likely should include women who are pregnant. The Methods section is well organised and described. The authors point out appropriately in the Discussion the challenges regarding socio-ethnic variables given the diverse nationalities in the control group. I agree that with the authors that a revised research project with clearer inclusion criteria to control for this likely would yield more informative data in the Qatar context. The authors correctly identify the high baseline prevalence of MetS in the Qatari population and control group - this likely renders difficult clear findings regarding the contribution of antipsychotic medication on the prevalence of MetS.

Thank you for your review. In fact, none of the women who participated in our research was pregnant.

Reviewer 2:

1. Page 3, Line 34. You may be able to expand on an idea you started here (that connects to your study directly), that certain race/ethnicities may be more or less at risk for antipsychotic-induced metabolic disease

Response: Thank you for this good idea. We added the following statement at the end of this paragraph on page 3 to introduce this aspect of our research:
“Thus, it seems that there are racial and cultural differences when studying the prevalence of MetS in patients with schizophrenia and maintained on antipsychotics.”

2. Page 3, Line 53. This is not an appropriate conclusion given it was an augmentation trial of sertindole. Metabolic parameters may not have been different but the group did not report MetS or account for the use of other, medical drugs which would meet criteria (e.g., anti-hypertensive therapy)

Response: Thank you for your remark. We deleted the statement and the reference as it is not directly relevant to our study. We added another reference that is more relevant in regard to the lack of increase in MetS in patients on antipsychotics. The section is now written as follows:

“However, other studies from Japan [13], Venezuela [14], and Italy [15] did not show that antipsychotics increase the risk of MetS compared to control subjects.”

3. Page 4, Line 34. this does not match your criteria listing at the end of the sentence

Response: Three figures were reported corresponding to three sets of criteria in the same sentence. The naming of the second criteria was expanded for clarification:

“A Kuwaiti study on schizophrenia inpatients showed prevalence rates of 18.8%, 23.2%, and 24.9% according to the ATP III, American Heart Association/National Heart, Lung, and Blood Institute (AHA/ATP III-A), and IDF definitions, respectively [25].”
4. Page 5, Line 14. citation? and how is your study different or adding to this study?

Response: The citation was written on the second sentence related to the same study. This study had only patients with schizophrenia and we elaborated further on the differences from our study in the “discussion” section. However, we modified the above statement to clarify this point as follows:

“One previous study from Qatar assessed patients with schizophrenia and showed a significantly higher prevalence of MetS (ATP III criteria) when compared to control subjects not receiving antipsychotics and with no mental illness (36.5% vs. 18.7%) [28]. Central obesity was the most commonly encountered risk factor among patients with schizophrenia compared to controls (63.9% vs. 45.7%) [28]. This study also included schizophrenia patients only, and thus few studies in the Arab countries have assessed directly the association of antipsychotics with MetS.”

5. Page 6, Line 4-7. Consider removing this extraneous information

Response: As suggested these lines were removed from the manuscript.

6. Page 6, Line 28. wouldn't this criterion bias you toward not finding MetS. How was this evaluated.

Response: We believe that you are referring to criterion (c) not known to have MetS. This issue was discussed extensively with the team after variable feedback during grant application. Qatar is known to have increased prevalence of MetS in the general population. We added this criterion to minimize the chances of recruiting more subjects with MetS as people known to have MetS
might be more willing to participate. We also applied this criterion to both the control group and to those receiving antipsychotics to equalize the chances of bias between the two groups. We did not do any screening test or measures to determine that they have MetS or not before enrollment, but we excluded those who were already known to have MetS as per their medical history or records.

7. Page 6, Line 39. State which diagnoses specifically?

Response: We included all psychiatric patients who were receiving antipsychotics. The specific diagnoses were reported under the results’ section: Psychiatric profile of the antipsychotics group:

“Patients who were on antipsychotics had mainly the following three diagnoses: bipolar (42.0%), schizophrenia/schizoaffective (35.7%), and depression (7.1%). The remaining 15.2% included the following disorders: personality, obsessive compulsive, delusional, psychotic not otherwise specified or mood not otherwise specified.”

8. Page 9, Line 19. what degree of correction

Response: As mentioned in the statistical analysis section, the level of significance was set at 0.05. The Bonferroni correction is an option in SPSS where the significance level is divided by the number of comparisons done for the different variables to control for the multiple comparisons.

9. Page 9, Line 53. Does this create a problem in group comparisons?
Response: The groups did not differ in regard to age and gender but there were other significant comparisons that we controlled for when studying the factors contributing to the presence of MetS in this sample as these might be affecting the prevalence of MetS and not necessarily the antipsychotics or psychiatric illness itself. Some of these significant comparisons were also discussed under the “limitations” section.

10. Page 11, Line 18. what was the distribution of other antipsychotics?

Response: The distribution of other antipsychotics has been added in the same section:

“The majority had history of multiple hospitalizations and were on SGA, where 43 subjects (38.4%) were on olanzapine, 36 on risperidone (32.1%), 17 on aripiprazole (15.2%), 12 on quetiapine (10.7%), 6 on paliperidone (5.4%), and 3 on clozapine (2.7%). In regard to FGA, 3 were on flupenthixol (2.7%), 4 on trifluoperazine (3.6%), 15 on haloperidol (13.4%), and 16 on chlorpromazine (14.3%). It is worth noting that 21 patients were on a combination of FGA and SGA, and few others were receiving more than two antipsychotics.”

11. Page 12, Line 4. what is the p-value?

Response: The p value for both criteria was added on the same page 12:

“The prevalence of MetS was higher in the antipsychotics group (31.9% for ATP III and 35.4% for IDF criteria) when compared to the control group (22.8% for ATP III and 29.8% for IDF criteria) (Fig. 2). However, this increase did not reach statistical significance, p = 0.12 for ATP III and p = 0.37 for IDF.”
12. a bivariate table would be useful to compare within groups

Response: We considered putting tables to report these analyses but we will need two tables (one for ATP III and one for IDF criteria and each table would have four columns (MetS vs. not for each of the antipsychotics and control group). Thus, we elected to summarize the results in one paragraph for both groups and to report the statistics for the significant results. However, if you think that it is better to add these tables, we have them ready and would be easy to add.

13. Page 12, Line 45. "and of last antipsychotic" what does this mean?

Response: In this sentence we are referring to the duration of last antipsychotic that was explained before in the section on Psychiatric profile of the antipsychotics group, last sentence:

“As many patients received multiple antipsychotics throughout the duration of their illness we calculated also the mean duration of the last antipsychotic received, which was over a year (Table 3).”

Furthermore, we re-wrote this sentence to make it clear:

“Bivariate analysis of the sociodemographic and clinical characteristics in the antipsychotics group alone showed that participants with MetS (vs. no MetS) had longer duration of illness (p < 0.05, ATP and IDF) and increased duration of treatment with the last antipsychotic (p < 0.05, ATP);”

14. Page 16, Line 26. important limitation since females may be at higher risk for MetS
Response: The ratio of male to females was not different in both groups but the number of females was lower in both groups. This was discussed on the same page comparing the possible differences in our study and the reported literature. We also mentioned in the last paragraph when discussing the limitations of our study.

15. Page 17, Line 28. you showed this?

Response: Our results showed that type of antipsychotics and equivalent dose of antipsychotics did not predict the occurrence of MetS in patients maintained on antipsychotics. In addition, there was no significant difference in the prevalence of antipsychotics when comparing FGA, SGA and combination of both. However, we realize that this was not the primary objective of our study and the number of subject in those categories was small. Thus, we modified that statement as such:

“Contrary to the general belief that SGA are more associated with MetS [11, 12], others have shown that polypharmacy and type of antipsychotics were not associated with increased risk of MetS in patients maintained on antipsychotics [42, 43]. Our results did not find any significant differences between those with MetS vs. not when comparing the type of antipsychotics and equivalent doses of antipsychotics.”