Author’s response to reviews

Title: The prevalence, metabolic disturbances and clinical correlates of recent suicide attempts in Chinese inpatients with major depressive disorder

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Author’s response to reviews:

Samuel Harris
Editor-in-Chief, BMC Psychiatry

Dear Professor Samuel Harris,

Please find a revised version of our manuscript “The prevalence, metabolic disturbances and clinical correlates of recent suicide attempts in Chinese inpatients with major depressive
disorder” in the attachment. The comments of the reviewers are highly insightful and have enabled us to greatly improve the quality of our manuscript. In the following pages are our point-by-point responses to each of the comments of the reviewers. Revisions in the text are highlighted by using blue color.

We hope that the revisions in the manuscript and our responses will be sufficient to make our manuscript suitable for publication in BMC Psychiatry. Please let me know if there is anything else we need to do with the revision, and we’ll prepare it as soon as possible.

We thank you very much for your excellent work. Your kind assistance is greatly appreciated. We look forward to any future correspondence.

Yours sincerely,

Tieqiao Liu

Reviewer reports:

Responses to Reviewer 1

Nela Pivac (Reviewer 1):

This is a nicely written article, very precise and short, showing potential clinical and biological risk factors of suicide attempts in a Chinese Han inpatient with MDD. This study confirmed previous data obtained in different ethnicities and different psychiatric groups that in Chinese MDD patients, low cholesterol levels was significantly associated with suicidal attempt. The authors also found longer duration of illness, more psychotic symptoms, lower LDL cholesterol and lower total cholesterol in patients who made suicide attempts compared to non-attempters with MDD. The whole manuscript is written well, with Introduction that covers the necessary data, Methods and Results are described adequately, the statistical analysis is in order, authors also used Bonferroni correction, Discussion is written very good.

I have almost no comments that would improve this manuscript. My recommendation is to accept this article after a really minor revision. My comments are listed below for Discussion, suggesting to the authors to cite other data that also showed lower cholesterol levels in suicidal patients.
Minor comments:

Question 1 : Discussion: When the authors are citing studies showing low cholesterol levels in patients, page 8, lines 48-54, please add also other study that found similar results: "For example, schizophrenia patients who had attempted suicide were found to have lower total cholesterol when compared to those without suicide attempts [36], and another recent study found lower level of serum cholesterol in suicidal male patients with bipolar disorder [37]." Please add: "In addition, lower cholesterol levels were detected in suicidal compared to non-suicidal patients with first episode of psychosis (Marcinko et al., 2007).


Answer:

Thank you very much for your positive comments and for your excellent suggestion. We have included this information as suggested, showing on page 8-9 (line 210-212) as "In addition, lower cholesterol levels were detected in suicidal compared to non-suicidal patients with first episode of psychosis[36]."

Question 2 : On page 9, lines 29-36, the authors discuss the association between 5-HT system and cholesterol. They might want to cite the article that simultaneously determined peripheral, platelet serotonin concentration and serum cholesterol concentrations in suicidal and non-suicidal patients with first episode of psychosis (Marcinko et al., 2007).: "Cholesterol levels have also been linked to alterations in levels of serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF), which is associated with suicide risk [45]." In line with these data, reduced cholesterol levels and reduced platelet serotonin concentrations were detected in suicidal compared to non-suicidal male patients with first episode of psychosis (Marcinko et al., 2007).

Answer:

This point is excellent. As suggested, we have added the information to the discussion section, on Page 9-10 (line 234-236), showing as "In line with these data, reduced cholesterol levels and reduced platelet serotonin concentrations were also detected in suicidal compared to non-suicidal male patients with first episode of psychosis[36]."

Thanks again for your positive comments and suggestions.
Responses to Reviewer 2

Giuseppe Carra (Reviewer 2):

This cross-sectional study is supposed to explore the prevalence, metabolic disturbances and clinical correlates of recent suicide attempts in Chinese inpatients with major depressive disorder. It concludes claiming an association between low plasma cholesterol level and recent suicidal attempt in patients with MDD.

Question 1: Not sure what the abstract means in terms of "Our findings suggest that the prevalence of suicide attempt in Chinese inpatients with depression is higher than that in the general population."

Answer:

Thanks for pointing this out. Since it has been well documented that the prevalence of suicide attempts is higher in subjects with depression than general population. We have deleted this sentence from the Abstract on page 2.


Answer:

Thank you very much for your comments. This point is excellent. Indeed, it is controversial about the association between lipid profile and suicide in mental disorders. We have cited these three articles mentioned by the reviewer and further explored the possible reasons of these
heterogeneity. We have added the following content in the discussion section on page 9 (line 213-225), showing as “While these findings make a strong case for an association between low total cholesterol level and suicidal behavior, other studies have reported no association between serum cholesterol and suicide [38-42], or association in the opposite direction [20,43]. The first possible explanation for these inconsistent results may be due to different time frames for suicide among different studies. For example, our study only included recent suicide attempts, while the others evaluated the lifetime suicide attempts [40]. Second, different definitions for suicide have been used in previous studies, including suicidal thoughts or ideation, plans, and death [20,38,43]. Third, in our current study we focused only on major depressive disorder, excluding those bipolar disorder [40], general population [20,43] and other mental disorders [38-39, 42], which are different from the previous studies. Fourth, other associated factors with suicide attempts were not included in most of previous studies, while our current study included several new clinical and psychological factors. Fifth, different methods to assess suicide attempts were used in previous studies. Finally, racial differences should also be considered.”

In addition, caution should be given in interpreting our results. We have added the following content in the discussion section on page 11 (line 279-282), showing as “However, owing to the limitations of a relatively limited sample size and cross-sectional design, our findings should be interpreted with caution and the results need be confirmed in a larger sample size using a longitudinal design in the future.”

Question 3: Also validity of measures used for MDD and of the definition of attempted suicide is really questionable. Extensive more work is needed in order to make the manuscript publishable.

Answer:

These points are very excellent. Regarding the validity of the diagnosis for MDD, two psychiatrists with more than ten years of clinical experience independently assessed the patient's psychiatric history and made a diagnosis for the same patient according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) criteria. We have added this information to the Methods section on page 4 (line 102-104), showing as “two psychiatrists with more than ten years of clinical experience independently assessed the patient's psychiatric history and made a diagnosis for the same patient according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) criteria.”

About the definition for attempted suicide, we used recommended definition to assess suicidal attempts. And we have added it in details to the Methods section on page 5 (line 123-126), showing as “Suicidal attempts were defined as a seriously self-destructive act with the intention of ending one's life but not resulting in death and excluded suicidal idea or all self-injury
behaviors without the 'intention' to die, as well as the low-lethal self-harm behaviors.” (Carrà G, Bartoli F et al., 2014)

Thanks again for all of your comments and suggestions.

Responses to Reviewer 3

Suhaila Ghuloum (Reviewer 3):

Question 1: The running title could be modified to better reflect the main objective of the study.

Answer: Thank you very much for this suggestion. We have modified the running title as “Cholesterol and suicidal attempt in depression”. (Page 1)

Question 2: There are several linguistic and grammatical errors throughout the manuscript which need correction. Examples include the first paragraph of "introduction" where it says 'risk factors for suicide attempt in MDD patients have still been unclear', the sentence could be corrected to '... are still unclear'. In the same paragraph, 'unemployed' should change to 'unemployment'. Also, the first sentence in Page 5 starts with 'which was'; this needs to be corrected depending on what the authors meant.

Answer: Thank you very much for these careful reviewing. We have corrected these errors. Also, we have also double checked the linguistic and grammatical issues in the present study.

Question 3: The authors describe one of the main aims of their study being exploring 'possible clinical and biological risk factors of suicide attempts'. However, the factors they explored are not inclusive of all those studied in the literature.

Answer: This point is excellent. We have added this point to the Discussion section on Page 11(line270-273), showing as “Finally, suicide related behaviors are complex and multifaceted phenomenon, which may associated with many other clinical and unknown biological factors. However, the factors that we explored are not inclusive of all those studied in the literature”.

Question 4: The definition of Suicide Attempt they chose is not referenced. Restricting the definition to the intention to end life is a subject of debate. It is not clear if in their recruitment of cases they indeed excluded all those with self-harm without the 'intention' to die.
Answer: Thank you very much for your comments. This point is very excellent. In our study, we considered suicide attempt as a seriously self-destructive act with the intention of ending one's life but not resulting in death. In order to limit potential misclassification bias, we excluded suicidal idea or all self-injury behaviors without the 'intention' to die, as well as the low-lethal self-harm behaviors. This is a recommended definition to assess suicidal attempts. We have added a detailed definition of suicide attempt to the Methods section on page 5 (line 123-126), showing as “Suicidal attempts were defined as a seriously self-destructive act with the intention of ending one's life but not resulting in death and excluded suicidal idea or all self-injury behaviors without the 'intention' to die, as well as the low-lethal self-harm behaviors[30].”

Question 5: Of the scales used, is there a validated version available in the local Chinese language? The authors need to explain if translated and culturally-adapted versions were used.

Answer: Thank you very much for pointing this out. The scales used in this article included The Self-Rating Depression Scale (SDS), Self-Rating Anxiety Scale (SAS) and Eysenck Personality Questionnaire (EPQ). All of these scales have validated Chinese version, which are widely used in China. Based on the comments of the reviewer, we have added this information in the Methods section on page 5-6 (line 136-137), showing as “All of the scales used in this study have Chinese version, have good reliability and validity, and also have been widely used in China.”

Question 6: Under methodology, there is no sample size calculation nor specification of duration of data collection.

Answer: Thanks for your excellent suggestion. In the present study, the sample size was calculated using the formula, $n = \frac{Z^2p(1-p)}{d^2}$. We have added this information in the Methods section on page 4-5 (line 110-115), showing as “The sample size was calculated using the formula, $n = \frac{Z^2p(1-p)}{d^2}[29]$. $Z$ was the degree of freedom at 95%, confidence interval being 1.96, $d$ was desired marginal of errored, set to 0.05, $p$ was the proportion of the population estimated to have a particular characteristic. According to a recent report in China, 23.5% of depressed patients had suicide attempt[28]. This gave a sample estimate of 276 patients. However, selected sample size of 288 depressed patients was used based on the duration of the study.”

In addition, we have added a detailed information about the specification of duration of data collection in the Methods section, under first paragraph of the subtitle-2.1 on page 4 (line 100-101), showing as “Two hundred and eighty-eight inpatients were recruited between June 01,2016 and May 01,2017.”
Question 7: The risk factors described and concluded are better referred to as 'associated factors'. In their statement of limitations, the authors acknowledge a causal relationship cannot be established.

Answer: This point is excellent. The expression of 'associated factors' is better than 'risk factors'. As suggested. We have replaced "risk factors" for "associated factors" in the whole article.

Thanks again for all of your comments and suggestions.

Responses to Reviewer 4

Taiane de Azevedo Cardoso (Reviewer 4): This is an interesting manuscript showing the factors associated with recent suicide attempts in an inpatient sample of individuals with MDD. The innovative aspect of the study is that they included only recent suicide attempts, and also that they are looking for an objective marker (blood biomarker) beyond the clinical characteristics. I have some suggestions to contribute for the improvement of this paper.

Question 1: Abstract: Authors described even the results that did not survive after the bonferroni correction. Please, keep just the significant results, which kept associated with the outcome in the regression analysis.

Answer: This point is excellent. We have added the results after the Bonferroni correction to the Abstract-result, showing as “Compared to those who had not attempted suicide, the suicide attempters had a significantly longer duration of illness, lower low-density lipoprotein (LDL) cholesterol, lower total cholesterol, and more psychotic symptoms. However, all these significant results did not survive after the Bonferroni correction (all p>0.05)”.

Question 2: Abstract: The first sentence of the conclusion is not needed. Because is very well documented that the prevalence of suicide attempts is higher in subjects with depression, as compared to general population.

Answer: Thanks for pointing this out. Indeed, it has been well documented that the prevalence of suicide attempts is higher in subjects with depression than general population. According to the suggestion, we have deleted the first sentence that“Our findings suggest that the prevalence of suicide attempt in Chinese inpatients with depression is higher than that in the general population” from the conclusions section of Abstract on page 2.
Question 3: Keywords: I would suggest including "metabolic disturbance" as a keyword.

Answer: Thank you very much for this suggestion. As suggested, we have added “metabolic disturbance” as a keyword on page 2.

Question 4: Introduction: In the end of the first paragraph: "Previous studies reported that the risk factors included: gender…". Please, specify the direction of the association. Women or men presented higher proportion of suicide attempts?

Answer: Thank you very much for such careful reviewing. Detailed information about direction of the association between gender and suicide attempt have been provided in the introduction section on page 3 (line 68), showing as“Previous studies reported that the risk factors included male gender [7]”.

Question 5: Introduction - Aim: Please, replace "risk factors" for "associated factors", considering that the current study is cross-sectional, and you can not determine the risk factors.

Answer: Thank you very much for this suggestion. The expression of 'associated factors' is better than 'risk factors'. We have replaced "risk factors" for "associated factors" as suggested.

Question 6: Introduction: The authors should include in the introduction the importance of this study, as well as what this study is adding to the literature.

Answer: Thanks for this suggestion. This point is very excellent. We have included this information as suggested, showing in the last paragraph of introduction section, on Page 3-4 (line 83-95) as "However, most previous studies focused on total cholesterol as a biomarker of interest, which might not be sufficient to display the relationship between suicide attempt and lipids. Hence, it is important to investigate the association between suicide attempt and lipid profile. The present study also included other blood markers, such as plasma glucose and thyroid hormone. Moreover, taking consideration about the duration from suicide attempt to blood sampling may impact the result, we only evaluated the suicide attempt in last month in this study. In addition, a recent study reported that suicide rates and the risk factors differed among countries [25, 26]. However, few studies that have investigated the prevalence of suicide attempts in Chinese people with depression revealed a wide range of prevalence (18.5% to 23.5%), with inconsistent associated factors[27, 28]. Thus, it is necessary to clarify this difference between different races. Therefore, the main aims of our study were to investigate the prevalence of recent suicide attempts in MDD inpatients, and the possible clinical and biological associated factors of suicide attempts in a Chinese Han inpatient population with MDD. "
Question 7: Methods - sample: It is not possible the comorbidity between MDD and bipolar disorder, as well as between MDD and schizophrenia. I suggest to the authors to reword the sentence in the inclusion criteria #5 for: "do not have the diagnosis of bipolar disorder, schizophrenia, alcohol or substance use disorders or other psychotic disorders."

Answer: This point is very excellent. Then we have rewritten the sentence in the inclusion criteria 5 of the Methods - sample section on Page 4 (line 105-107), showing as "5) Patients who are not diagnosed with depressive episode of bipolar disorder or post-schizophrenia depression, and no co-morbidity with alcohol or substance use disorders or other psychotic disorders;"

Question 8: Methods: In the end of page 4, when authors describe the clinical variables assessed, there is incomplete information - "family history". Please, complete. Did you assess the family history of mental illness?

Answer: Thanks for pointing this out. We apologize for this uncertain description. Yes, we completed the assessment of the family history of mental illness for all patients. This incomplete information - "family history" has been changed to "family history of mental illness" on page 5 (line123).

Question 9: Methods: Please, clarify how did you perform the bonferroni correction, in the last sentence of the methods. Did you divide the p-value by the number of comparisons?

Answer: Thank you very much for this suggestion. Statistical textbooks present Bonferroni adjustment (or correction) in the following terms. First, divide the desired alpha-level by the number of comparisons. Second, use the number so calculated as the p-value for determining significance. SPSS and some other major packages employ a mathematically equivalent adjustment. Here's how it works. Take the observed (uncorrected) p-value and multiply it by the number of comparisons made. Then compare the corrected P value with the set P value (alpha set at 0.05). We have added this information in the last sentence of the methods, on page 6 (line 160-162), showing as “Bonferroni corrections were used to account for multiple testing, which were performed through multiplying the unadjusted P value by the number of comparisons made to obtain the adjusted P value, compare it with set P value (0.05)’’.

Question 10: Results: Would be better "methods of attempt" instead of "means of attempt", in the beginning of the fourth sentence.
Answer: Thank you very much for the suggestion. We have replaced "means of attempt" for "methods of attempt" in the beginning of the fourth sentence of results on page 7.

Question 11: Results: There is some confusion in the description of results about correlation. The authors described correlation including categorical variables, such as: recurrent depressive episode, presence of psychotic symptoms, and suicide attempts. We can just perform correlation test using two continuous variables. Please, justify it.

Answer: Thank you very much for pointing this out. In our study, the relationship between recurrent depressive episode, presence of psychotic symptoms, and suicide attempts were performed by chi-square test instead of spearman correlation analysis. We have corrected the statement in the right way. The chi-square test results are shown in the result section on page 7 (line 176-177) as “higher rate of recurrent depression ($\alpha^2=3.86$, $p=0.05$), more psychotic symptoms ($\alpha^2=4.67$, $p=0.03$)”. We have removed the correlation results of classification variables in the result section on page 7.

Question 12: Results: In the end of the results, please replace the "significant predictors" for "significantly associated with".

Answer: Thank you very much for the suggestion. Indeed, "significantly associated with" is a better expression. We have replaced "significant predictors" for "significantly associated with" in the end of the results on page 7(line 184).

Question 13: Discussion: In the first paragraph, I suggest to include "associated with suicide attempts" in the following sentence: "This was an exploratory cross-sectional clinical study, examining the socio-demographic, clinical characteristics and biochemical parameters associated with suicide attempts in Chinese inpatients…"

Answer: Thanks for pointing this out. We have added "associated with suicide attempts" in the first paragraph of discussion on page 8 (line 188). Showing as "This was an exploratory cross-sectional clinical study, examining the socio-demographic, clinical characteristics and biochemical parameters associated with suicide attempts in Chinese inpatient subjects…”

Question 14: Discussion: Also, in the first paragraph of the discussion, please include just the results that kept associated with the outcome in the adjusted analysis.
Question 15: Discussion: I think that the authors can remove the second paragraph. Because they cannot compare their results about the prevalence of suicide attempts with the general population. They can just compare with studies including MDD samples, as described in the third paragraph.

Answer: Thank you very much for pointing this out. We have removed the second paragraph in the discussion section.

Question 16: Discussion: In the end of the third paragraph, the authors described that the variability regarding the prevalence of suicide attempts among studies may be related to the differences in the definition of suicide attempt used, sample selection, and the duration from suicide attempt to blood sample. I suggest to remove this part regarding the "blood sample", because it did not interfere in data regarding prevalence of suicide attempt.

Answer: This point is very excellent. Based on the suggestion of the reviewer, we have removed that "the duration from suicide attempt to blood sample" from the variability reason of prevalence of suicide attempt among different reports. (on page 8)

Question 17: I think you do not need to discuss about the methods of suicide attempts (paragraph #4), because it was not the main aim of your paper.

Answer: This point is excellent. We have deleted this paragraph about discussing about the methods of suicide attempts.

Question 18: Strengths of the study are missing in the discussion. Please, elaborate it.

Answer: This point is excellent. We have included this information as suggested, showing in the last paragraph of discussion section, on Page 10 (line 250-254) as “The first strength of this current study was that we focused on recent suicide attempts, which made the correlation results more accurate and avoided the impact of the duration from suicide attempt to blood sampling. Another strength was that we assessed the objective blood markers for suicide attempt rather
than only the clinical characteristics, which few studied examined in the Chinese Han population before.”

Thanks again for these careful reviewing and all of your suggestions.