Author’s response to reviews

Title: Alterations of serum macro-minerals and trace elements are associated with major depressive disorder: a case-control study

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Author’s response to reviews:

Reviewer-1 (Cathy Levenson):

Comment 1:

I. Abstract:

The abstract states that the goal to determine serum levels of metal and minerals and to "discover their role in depression". While it is an excellent goal to understand the role of these metals, only serum levels were measured in this work. Since there is no data collected on their role in depression, this sentence should be modified.

Response:

In abstract the sentence has been modified as “The purpose of the study was to determine the serum levels of MM (calcium and magnesium) and TE (copper, iron, manganese, selenium and zinc) in MDD patients and find out their associations with depression risk”. This revision can be viewed in abstract section, line 29-31, and page 2.
Comment 2:

II. Background:

1. The first page of the background section deals with symptoms and incidence of depression. Given that the focus of this paper really is trace elements, this is too much information on the incidence of depression. This section needs to be cut considerably as it is likely that readers of this journal are very familiar with depression, but less familiar with the possible role of these elements in depression.

Response:

The first page of the background section has been shortened considerably by removing the redundant information.

Comment 3:

2. Cutting the description of the incidence of depression would leave more room for an introduction to the known role of these trace metals in depression. As it is currently written, it is not clear if the mechanisms mentioned are known to play a role in depression. For example, three different forms of SOD are discussed. Are all of these forms known to play a role in the mechanisms of depression? This is just one example - this page would be more helpful to readers if it specifically addressed mechanisms of minerals and metals in depression that provide a rationale for measuring these elements.

Response:

After removing the information regarding symptoms and incidence of depression from background section, the known roles of all the analyzed trace metals in depression have been introduced one by one. At first, the role of macro-minerals (calcium and magnesium), then the role of trace element (copper, iron, manganese, selenium and zinc) and finally the role of metallo-enzyme, superoxide dismutase (SOD) in depression have been described. This revision can be viewed in background section, line 50-79, and page 3.

Comment 4:

3. The third page of the Background section finally addresses the role of minerals and metals in depression, but again it is not really specific enough. For example, it is stated that Cu plays a major role in "chronic mental illness". What role? What illness?

Response: The known role of all analyzed minerals and metals in depression is addressed more specifically in revised manuscript. Moreover, the role of superoxide dismutase(SOD) in depression is also described in revised version. This revision can be viewed in background section, line 66-69, and page 3 and 4.
Comment 5:

4. It is not clear why schizophrenia is relevant in a paper on depression. Panic and anxiety disorders are relevant given that 80% of people with depression and also have anxiety, and 90% of people with anxiety are depressed. But the link to schizophrenia seems less clear and probably should be edited out.

Response:

Information related to schizophrenia has been eliminated and the manuscript is revised focusing on the association of trace elements and micro-minerals with depression.

Comment 6:

III. Results and Discussion

1. Do alterations in mineral and metal status lead to depression? Or does depression lead to an alteration in nutrient status and thus an alteration in mineral and metal serum levels? While there appear to be statistically significant differences between the patients and the control group for all of the elements measured, none are outside of the reference range. This suggests that rather than a cause of depression, the altered mineral status is the result of the depression.

2. The first paragraph of the discussion suggests that these data could be used for diagnosis and treatment. Given that all the values were within the reference range for both control and MDD, I do not see how this would be used for diagnosis. There is also no indication for treatment if the values are not outside of the reference range.

Response:

Statistically significant differences between the patient and the control groups were observed for all the elements measured but none were outside of the reference range. So we have revised our comments regarding diagnostic value and treatment outcome of our findings in first paragraph of discussion section as “The present study explored the associations of MM and TE with the risk of major depression, demonstrating that alterations of serum MM and TE levels were associated with an increased risk of MDD”. Also, discussion section has been reorganized element by element and our study results have been compared with earlier research findings. For this, at first we discussed about macro-minerals (calcium and magnesium), then trace element (copper, iron, manganese, selenium and zinc). This revision can be viewed in discussion section, line 172-174, and page 8.

Reviewer-2 (Zdenka Durackov):

Comment 1:
- Background is described chaotically and difficult to read. Authors skip from one element to another, and then add more insights into the elements. E.g. On page 4 there is mentioned SOD in lines 4, 13 and then 20-23, and other enzymes with Zn, Ca as a signal element, etc. are mentioned among the SOD information.

- I recommend choosing how to present information - either by element or - by disease and effect.

Response:

Background section has been shortened considerably by removing the redundant information. Then the known roles of all the analyzed trace metals in depression have been introduced one by one. At first, the role of macro-minerals (calcium and magnesium), then the role of trace element (copper, iron, manganese, selenium and zinc) and finally described the role of metallo-enzyme, superoxide dismutase (SOD) in depression. This revision can be viewed in background section, line 50-79, and page 3.

Comment 2:

- In addition, FeSOD is a SOD isoform that does not occur in humans and therefore I recommend not to mention this form.

- If the authors at one point indicate SOD as CuZn SOD, then they should not use the SOD1 in another place and the same for MnSOD and SOD2 p. 4).

Response:

Iron containing superoxide dismutase (SOD) has been omitted in revised manuscript.

Section related to SOD has been revised without reappearance of same information as “Superoxide dismutase (SOD) is a metallo-enzyme that contains metal ions in its structure. In human, three types of SOD are present. SOD1 is cytoplasmic, SOD2 is mitochondrial and SOD3 is extracellular. SOD1 is a dimer while SOD2 and SOD3 are tetramers. SOD1 and SOD3 contain Cu and Zn, while SOD2 contain Mn at their reactive center. CuZnSOD involved in defense against reactive oxygen species (ROS). MnSOD is an antioxidant enzyme that provides protection against free radicals”. This revision can be viewed in background section, line 82-87, and page 4.

Comment 3:

- To arguments on p. 5, lines 2-5 add citations.

Response:
This section has been revised and the known role all the analyzed trace elements have been described with proper citations. This revision can be viewed in background section, line 66-69, and page 3 and 4.

Comment 4:

- A lot of information is about schizophrenia and little about the depressive disorder.

Response:

Information related to schizophrenia has been eliminated and the manuscript is revised focusing on the association of trace elements and micro-minerals with depression.

Comment 5:

- Explain all the abbreviations used in the text for their first use, even if they are listed in the "Explained Abbreviations" section - the reader is better oriented (GAD - p. 6, line 2).

Response:

All the abbreviations have been explained in the text for their first use in the revised manuscript.

Comment 6:

- Statistical analysis: Author used t-test and Pearson's test. Did authors track normal/out of normal data distribution?

Response:

Parametric tests (t-test and Pearson correlation coefficient) have been used for the normality of data distribution and it is mentioned in “statistical analysis" section.

Comment 7:

- Table 1: explain abbreviations - CED, KBDT in the text below the table

Response:

Abbreviations of CED and KBDT have been included in the text below the table-1. This revision can be viewed in table section, line 302, and page 14.
Comment 8:

- Discussion: The authors argue that the concentration of MM and TE ... are strongly associated with MDD .... However, since they did not evaluate the correlations between the levels of the individual elements and the psychiatric score characterizing the severity of depression, the claim is premature. Re-formulate it.

Response:

This section in discussion has been revised as “The present study explored the associations of MM and TE with the risk of major depression, demonstrating that alterations of serum MM and TE levels were associated with an increased risk of MDD”. Also, discussion section has been reorganized element by element and our study results have been compared with earlier research findings. For this, at first we discussed about macro-minerals (calcium and magnesium), then trace element (copper, iron, manganese, selenium and zinc). This revision can be viewed in discussion section, line 172-174, and page 8.

Comment 9:

- English needs correction

Response:

English language has been edited.