Reviewer’s report

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

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Reviewer: Cathy Levenson

Reviewer’s report:

The issue of trace metals in major depressive orders is an important and clinically relevant area of inquiry. A strength of this paper is that it seeks to look at a large group of minerals and metals rather than single elements.

A second strength is the attempt to look at potential interactions between the metals.

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.

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.

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.

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?

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.

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.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
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No

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