Author's response to reviews

Title: Vitamin D deficiency and psychotic features in mentally ill adolescents

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Author's response to reviews:

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Re: MS 2135263157648964 “Vitamin D deficiency and psychotic features in mentally ill adolescents”

To the editor:

We appreciate the careful review and thoughtful comments provided on our submitted manuscript: Vitamin D deficiency and psychotic features in mentally ill adolescents”, and list our responses below.

We note that the changes made have improved the paper and are grateful for the efforts put in by the reviewers.

Please find our revised manuscript uploaded.

Response to Reviewer 1 comments:

Minor essential revisions:

1. Why did the authors stick only to psychosis and not include mood symptoms?

We agree it would have been of interest to examine mood symptom severity in relation to vitamin D levels in addition to psychosis. We were unable to do so beyond examining association and clinical diagnosis, for several reasons: there were no structured diagnostic interviews performed; no standardized mood rating scales were available routinely, and this was a small clinical convenience sample under budget limitations. We plan to perform mood ratings prospectively in an inpatient population in the future.

2. Table 1 patient characteristics are reported in an unusual way; why not just given the number in one category and the % in parenthesis?

Yes/No values have been changed to N, % for the appropriate data, as possible, for Table 1 in the revised manuscript.
3. The quality of the figures needs to be improved and the numbers at the bottom seem lost from the figures.

The figures are autogenerate by SAS; we have uploaded newer figures and unfortunately the new uploads represent the best figures we can obtain. The numbers at the bottom have been moved in keeping with the style of the journal and will now be as legend data under the figure title.

4. The paragraph on demographics and other related variable differences is dense; could the section be divided and each point made more clearly?

The paragraph has been subdivided and points articulated more clearly.

5. There should be a discussion on vitamin D and mood.

Given the length of the discussion, lack of pure mood data, and focus on psychotic symptoms as the primary outcome variable in a small sample, we felt it in the best interest of the paper to limit the discussion to the key variable of concern, especially since we had no valid measurements for mood severity symptoms. We do state in the discussion in several places that the underlying diagnoses appear to be predominantly mood disorders, and provide references about small clinical samples, vitamin D deficiency, and depression.

6. The sentence “Our finding was recently replicated in the pediatric population” is a little odd- doesn’t this study replicate other findings?

We had mentioned our finding as ‘recently replicated in the pediatric population’ due to chronology of the reports; the collection and presentation of our data as a poster occurred prior to the collection and presentation as a poster by Zhang et al. This has been clarified by changing the language within this statement to “Our findings also agree with an unpublished 2011 report of a child and adolescent psychiatric population residing in the Pacific Northwest”, and by including an abstract reference documenting the presentation of our data as a poster a year earlier than the Zhang reference. The text clarifies that the Zhang data has not undergone peer review and is an unpublished abstract.

Response to Reviewer 2 comments

1. The number of patients with missing values was not described.

There were no missing data for the following: 25-OHD levels, gender, race, living location, insurance type, inpatient vs. outpatient status, psychosis, immediate and extended family history of psychosis, primary diagnosis, and medication use. Missing data were present for the following: BMI N=4, glucose N=5, Cholesterol and HDL N=50, LDL N=49, TG N=49, pulse N=4, DBP, SBP N = 5, calcium N=6, height N=4, waist circumference N=50, weight N=3.

This information has been added to the footnotes for Table 1.

2. Concern about small potentially unrepresentative sample, oversampling of winter months, location, and potential confounding of psychosis with lack of access or reticence to seek care early.
We have added to the limitations section a statement that winter months were oversampled.

Controlling for season did not find a difference and was not included in our table but was mentioned in the text. Studies of vitamin D levels in Southern latitudes find similar rates of vitamin D deficiency, likely due to changes in diet and lifestyle. We have added a reference clarifying the relationship of UV radiation across months.

We have previously addressed the points brought up by the review as follows:

a) Location: top of page 9

“Our higher prevalence rates of deficiency and insufficiency may be in part due to the latitude of Rochester, NY, 43.145 degrees N. Paris, France is 48.51N, and Geelong, Australia 38.10S. Except during summer months, skin makes negligible vitamin D from sunlight at latitudes above 37 degrees north or below 37 degrees south.”

b) Small and possibly unrepresentative sample: page 12

“This work is limited by a small sample size, cross-sectional method, inpatient sampling bias, and lack of formal research measures for diagnosis and severity of illness, family psychiatric history, sun exposure, and intake of Vitamin D and other dietary nutrients.”

c) Confounding of psychosis with lack of access or reticence to seek care early.

The service utilization in Rochester NY provides prompt access of care for adolescents seeking admission due to both short lengths of stay and use of the partial hospitalization service. Admissions for severity of cases are prioritized. Waits for the partial hospital service are usually no more than several weeks and severity of cases are prioritized for admission. Adolescents presenting with severe distress to acute care may be more readily identified and brought for treatment due to the levels of distress they may be causing within their families and schools. Prospective longitudinal work will examine onset of symptoms and time to help-seeking as potential confounders. We do suspect that reticence to seek care early may be related to higher rates of vitamin D deficiency in the very small minority Asian sample, since all had psychotic features.

3. The discussion section could benefit from clarification and further justification of the conclusions drawn from existing data.

We have clarified the discussion, including using subheadings. We have also justified the conclusions more specifically in contrast to the existing data.

4. It would be worthwhile to expand on how this study fits in with and advances the existing literature.

We have outlined directions for future research and have also added a comment concerning the potential importance of clinically supplementing dark-complexion adolescents with vitamin D in the discussion.

Discretionary revisions
1. Note the sample sizes in figures 1a and 1b.
Sample sizes have been added.
2. Figure 2 would benefit from a more informative legend or by bar graphs
Information has been added to the figure legend adding to title explanation.

Minor essential revisions
1. The term ‘cohort’ is confusing since this is a cross-sectional study.
We have removed the word ‘cohort’ from the manuscript.
2. The authors referred to previously published work by other groups as confirming and replicating their own findings when the temporal relationship is reversed.
See 6. above; temporal relationships of the presentation of the data have been clarified.
3. Revise the discussion section to clarify and justify conclusions taking into account potential confounds; improve clarify and coherence especially when describing the relationship to existing published data.
We have clarified the discussion and added more information related to potential confounds; in addition, we have clarified how this paper contributes to the literature and is different than its predecessors on the same topic.
We appreciate the opportunity to resubmit this article with the revisions noted for reconsideration of publication.

If you have any further questions, please contact me at 614-722-3066 or at Barbara.Gracious@nationwidechildrens.org.