Reviewer's report

Title: Early Low Bone Mass in Schizophrenic Patients as Compared with Normal Populations

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Reviewer: Chittaranjan Andrade

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COMMENTS TO AUTHORS
Using ultrasonographic techniques, the authors found that, at younger ages, heel bone mass was lower in schizophrenic women than in community controls. Controversially, female schizophrenic patients had lower bone mass when their body weight was higher, and higher bone mass when their body weight was lower; and neither male nor female schizophrenic patients displayed the decrease in bone mass expected with aging. Specifically, older female schizophrenics had higher bone mass values than age-matched healthy female controls.

Major concerns:
1. In both abstract and discussion sections of their paper, the authors should clearly acknowledge the important limitations of their study: the use of ultrasonographic assessments instead of DXA scans, and the assessment of bone mass at only one location (heel). A special section in the discussion should more extensively address these and the other limitations of the study.
2. Abstract, results subsection: The first sentence, while numerically accurate, is unsupported by the statistical analysis. The low bone mass was significant only for younger female schizophrenics. The improvement in bone mass with aging was not significant in the trend analysis. The authors will need to reword this subsection based on the reanalysis suggested below.
3. Abstract and discussion: The survival selection hypothesis is far-fetched. It would make sense only if the advantage were present at a younger age, during the period of reproductive
fitness. I assume that the authors refer to survival selection in an evolutionary context.

4. In the conclusion subsection of the Abstract, the authors write that prevention strategies are indicated for schizophrenic patients. However, nowhere in their paper do they show that the risk of pathological fractures is elevated in schizophrenia; in fact, the risk may not be elevated, at all (see Andrade et al, J ECT 2007). This is a notable shortcoming, considering that the authors devote much space in their discussion and in the reference list to an explanation for the lower bone mass in schizophrenia.

5. In the Introduction section of the paper (Page 3), references 6-8 are unnecessary. It would be more appropriate to reference the many studies on bone mineral density and osteoporosis in schizophrenia (e.g., Hummer et al, Am J Psychiatry 2005; Meyer and Lehman, Ann Clin Psychiatry 2006). The findings of the present study should then be solidly discussed in the context of the literature on schizophrenia.

6. The methods section should describe how the community controls were sampled.

7. The use of multiple t-tests to compare schizophrenics and controls categorized by age group and gender vastly inflates the Type II error risk. These data should more appropriately be analyzed using MANOVA. For example, separate MANOVAs can be performed in each of the age by gender categories in Table 1. This analysis would, for example, indicate whether there is main effect for diagnosis in the schizophrenia vs control BUA values in men; and whether there is a significant diagnosis by age group interaction in the schizophrenia vs control BUA values in women. Alternately, the separate t-test values can be retained if a Bonferroni correction is applied.

8. The paragraph starting "The results shown in Table 1 ...." on Page 8 is unsupported by statistical inferences. The MANOVAs suggested above would remedy the deficiency.
9. Discussion, towards the bottom of Page 10 and again, towards the bottom of Page 11: "The reason may be the same as that of inadequate peak bone mass." "The same causes may then appear to have played a protective role ...." These statements are absolutely unacceptable. How can an explanation for lower bone mass in younger patients hold true as an explanation for an absence of decrease in bone mass with increasing age? If the authors are unable to explain the counterintuitive findings of an absence of a menopausal effect and an absence of a weight effect, they should note that their findings are inexplicable and require further study, and leave it at that!

10. Data on years of illness and use of medication should be provided if available, and used as a covariate in the analyses, if possible.

Other concerns:
1. The title of the paper is awkwardly worded. I'd suggest something like "Bone mass in schizophrenia across different decades of life".

2. The Results and Discussion sections should be separated.

3. In various places in the abstract, results, and discussion, attention has been drawn to results that indicate numerical differences in the absence of statistical significance. This is not good science.

4. Last two lines on Page 10: Is menopause really earlier in schizophrenia? If so, this should be referenced. Likewise, the lowering of sex hormones in schizophrenia should be referenced.

5. The term 'hyperprolactinemia' is more appropriate than 'prolactinemia'.

6. The data in Table 3 can be analyzed using Chi square tests on the absolute values.

**Level of interest**: An article of importance in its field

**Quality of written English**: Needs some language corrections before being
published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.