**Reviewer's report**

**Title:** Is there an association between elevated or low serum levels of phosphorus, parathyroid hormone, and calcium and mortality in chronic kidney disease patients? A meta-analysis

**Version:** 1  **Date:** 12 January 2013

**Reviewer:** Julia Scialla

**Reviewer's report:**

The authors have performed an updated systematic review and meta-analysis related to a topic of substantial interest in nephrology. The authors aimed to assess a limitation of other recently published systematic reviews in this area; namely, whether consideration of non-linearity between the relationships of calcium, phosphate, PTH and mortality in dialysis patients would result in different conclusions.

**Major Compulsory Revisions:**

1. Search strategy: the search strategy is not clearly defined. The details of the search strategy, and/or the deviations of the search terms from the prior review should be reported more precisely.

2. Dual data abstraction is generally preferred and is a limitation of this analysis.

3. Details of what data elements were abstracted is not provided. The data abstracted in table 1 is primarily qualitative in nature and does not include information such as sample size, effect estimates and their associated measures of variability, and other critical factors in observational studies, such as definition of the exposure (eg. single measures/average/time varying, assay where relevant, setting in which it was measured), covariates that were controlled for and "quality" scores. Although more detail is provided for the studies that qualify for meta-analysis, these findings would also guide the qualitative review.

4. In deciding which studies to include in a meta-analysis, the authors select studies with a referent category in the "middle" of the data distribution among other criteria. 86% of the studies are excluded from meta-analysis, leaving only 7 studies. It is possible that many studies that did not report non-linear models (or reported the lowest category as the reference) did so because exploratory data analysis did not strongly suggest non-linearity. It is difficult to distinguish this possibility from the author's valid concern that modeling in some cases may have been "naive". However, such exclusion would remove studies from the meta-analysis in which the relationships were approximately linear or merely flat, which could induce substantial bias.

5. The qualitative analysis largely counts the "score" of positive and negative studies without considering sample size, quality and adjustment in how these...
studies should be "weighted" during interpretation. Addition of quantitative information to Table 1 would guide a more descriptive discussion of all studies.

6. Despite the valid hypothesis that substantial non-linearity may have been missed in prior studies and biased prior meta-analysis, figures 3-5 do not suggest substantial non-linearity even in this selected subset. In each figure only one study appears to have a substantial "U-shape". Only in the case of phosphorus is this the largest study. In the meta-analysis, none of the lower than reference values have higher risk than reference and lower calcium has a lower risk, suggesting a dose response. Given that the observed deviations from linearity are modest overall, I question the premise that the studies that used linear models (or the lowest category as the reference) should have been excluded.

Discretionary Revisions:

1. Greater discussion of limitations mentioned above.

2. May be interesting to discuss the need for more detailed reporting in the nephrology literature to facilitate future meta-analysis.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I declare that I have no competing interests