Author's response to reviews

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

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Author's response to reviews: see over
February 19, 2013

Hayley Henderson
Executive Editor
BMC Nephrology

Dear Dr. Henderson,

On behalf of my co-authors, I am pleased to submit a revised manuscript entitled “Is there an association between elevated or low serum levels of phosphorus, parathyroid hormone, and calcium and mortality in end stage renal disease patients? A meta-analysis” to *BMC Nephrology*.

We would like to thank the Reviewers for their insightful comments, which have helped to strengthen the manuscript. We have been diligent in revising the paper based on the two reviewer comments. The revised manuscript includes all changes tracked in redline mode, and we also have included a point-by-point response to each Reviewer on the following pages.

We look forward to your guidance and to completing the revisions to the manuscript.

With best regards,
Jaime Natoli, MS, MPH
Corresponding Author
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: 4 January 2013

Reviewer: David Leaf

Reviewer's report:

Major Comments

1. Page 8: “We did not attempt to contact study authors to inquire about missing data or exact values of graphical elements.” Why not? This would have strengthened the study.

   We agree that contacting the authors to inquire about missing values would have had the potential to strengthen the study. From past experience we found that corresponding authors on published papers do not always respond to new data inquiries and often do not have the time or resources to extract their data and provide those results to us in a way that was analyzable. Furthermore, our research team had limited resources. Consequently, we felt it was best to expend our limited resources on analyzing the studies available.

2. Page 32-38: Table 1, which is 7-pages long, would be more appropriate as supplementary material.

   We have received conflicting reviewer comments on this table. In contracts to this Reviewer’s suggestion, Reviewer #2 suggested we expand this table with additional details. We believe Table 1 is important to the paper and would prefer to keep it in the main text rather than minimize it as an Appendix. We have some additional thoughts regarding this table, which are noted in the response to Reviewer #2.

3. Page 41-42: It is not necessary to provide the definition of “risk ratio.” An educated reader will know what this means. Similarly, it is not necessary to define that “if the confidence interval contains 1, the RR is not statistically significant.”

   Thank you for this comment. We have removed this text following the CI definition and edited out most of the explanatory text on the RR definition as we wanted to have some guidance to the clinical reader but agree that all of the original text was not necessary.

4. Page 43: It appears that there is an error here. The 95% CI for low PTH contains 1, however, the p value is significant. On the other hand, the 95% CI for high PTH does not contain 1, yet the p value is not significant. Perhaps the authors mistakenly switched the p values?
Table 5 is correct here. However, we agree that in its original form it was confusing. The p-value refers not to the risk ratio but to the Q statistic (and the degrees of freedom also referred to the Q statistic). Given the reviewer comments, we have decided to omit the Q statistic results entirely and we feel the new Table 5 is easier to interpret now.

Minor Comments

5. Throughout the manuscript, including the title, the authors use the term “chronic kidney disease.” However, their study population is limited to patients with end stage renal disease on dialysis. In general, the term “chronic kidney disease” refers to patients who are predialysis. Therefore, their use of the term in this manuscript is misleading. They should replace this with “end stage renal disease (ESRD)” or “end stage kidney disease (ESKD).”

6. Page 4: it is redundant to say “ESRD” and also “requiring dialysis.”

We appreciate these comments. A subtle but important point that we wanted to stress is that some ESRD patients are not on dialysis because they have received kidney transplants. Kidney transplant patients were not included in the studies that were meta-analyzed however. Therefore, we have now changed the text to say “end stage renal disease (ESRD)” but have chosen to keep the words “on dialysis” for clarity.

7. Page 4: “Nevertheless, a qualitative assessment of the studies led them to conclude that abnormalities in certain biochemical parameters…” The authors should specify what kind of abnormalities. High or low?

Covic et al found higher values of all 3 biochemical parameters to be associated with all-cause mortality and also found evidence to support low phosphorus to be associated with increased mortality risk. We have modified the sentence to better clarify their findings.

8. Page 5: It is highly unorthodox to refer to figures in the introduction.

We agree that presenting a figure that explained the results of the study would be inappropriate in the Introduction, we note that the figure in question is not based on the results but rather is an explanatory figure designed to give the reader a better perspective on the rationale for our study (particularly the Methods, which were more advanced than a traditional meta-analysis). We have therefore decided after much thought to leave the figure in the paper as is.

9. Page 13: last paragraph of the results section. The authors should avoid speculating in the results section. This is more appropriate in the discussion section.

We have edited this paragraph and the Discussion substantially to address your concerns.

10. Page 13-16: It is unorthodox to refer to tables in the discussion.

We have edited the Discussion to address this comment.
11. Page 14: the authors should soften the wording where they state, “The lack of statistical significance for lower values of phosphorus and PTH is partly attributable…” Instead, they might consider writing, “The lack of statistical significance…MAY BE partly attributable…”

We have made the suggested change in wording.

12. Page 43: it is not necessary to provide the Q statistic and the degrees of freedom. The Risk ratio, 95% CI, I2 statistic, and p value are sufficient.

We have removed the Q statistic from Table 5.

Thank you for your detailed reading of our manuscript and for the comments you have provided.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

None
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.

   We have provided our search strategy as an appendix to the document and we have included some brief elaboration on the nature of the search terms in the main text.

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

   Although independent, blinded, dual data abstraction is the “gold standard” for systematic reviews/meta-analysis, limited resources meant that we used a single abstractor with QC by a second researcher. However, we do not believe that this approach had a perceivable impact on our results or conclusions. We have added a sentence to the Discussion to address this limitation.

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.

   We have received conflicting reviewer comments on Table 1. Although this Reviewer was interested in additional detail, Reviewer #1 suggested that this be moved to a supplemental
appendix. We believe Table 1 is important to the paper and would prefer to keep it in the main text of the manuscript. However, given the size of the table (51 rows), we hesitate to add a substantial amount of additional information. We have added some high-level information on each study, including the study/database name, study design, follow-up duration, dialysis vintage, dialysis type, and sample size. We also have simplified the qualitative information on each study's attempt to explore non-linear relationships, graphical depictions, etc.

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 "naïve". 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.

This is a very insightful comment and we are appreciative for it. We have no way of knowing what, if any, analyses were done and not reported in the included studies (i.e., reporting bias). While it is possible that some studies tested for non-linear relationships, found none and did not report this finding, and then let this finding guide their modeling, we think that this is unlikely. When a predictor is modeled as a continuous variable (e.g., age) the assumption is that lower values (e.g., younger patients) do “better” in terms of outcome (or there is a dose effect where more of the dose increases the risk of getting the outcome of interest etc). Clinically, it is not plausible that very low values of some of the biomarkers (particularly phosphorus and PTH) are “healthier” than clinically agreed upon “normal” values –and yet that is how these variables have often been modeled. So while it is possible that a reporting bias exists in that only the “significant” non-linear results are reported and then subsequently meta-analyzed in our study, we feel it is more likely that naïve modeling was the reason why non-linear relationships were not observed and this type of modeling prevents us from combining these studies with those which modeled the referent category as the “normal” or “middle range” value.

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.

See response above regarding additional details for Table 1.

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.

The reviewer brings up several important points. First, we stress in the paper that there is not always a U shape but a J shape present in the data as very low biochemical marker values are often rarely encountered making it hard to have the left part of the “U” visible. The reviewer astutely notes that the larger studies do show a more non-linear, “U” shaped result. We also note in the manuscript that the lower dose values are non-significant which may be partly due to sample size. Clinically, it is not plausible in our opinion that abnormally low PTH and phosphorus values (which are naturally occurring biomarkers) would be “healthier” than values found in the “normal” range of adults. However, abnormally low values are rare and so power is an issue in this analysis.

Next, we would point out that from a methodological perspective, combining studies with different referent groups for a meta-analysis (especially given the limited amount of reported data) is quite difficult if not impossible because the risk ratios have different meanings between studies. We have given much thought on how best to do this admittedly complex meta-analysis and how to include as many studies as possible and believe our approach is valid. Notably if a study made the “normal” range the referent and then found no difference in high or low values, that study would not be excluded from our analysis preventing a selection bias. Furthermore, as we say in our Discussion, when studies did model a biochemical parameter as both a continuous, linear predictor and then as a categorical variable, the risk ratios were more extreme with the categorical approach. Thus, combining continuous and categorical results in a meta-analysis would be at best misleading.

A key point of our study is that if a non-linear relationship exists between the biomarkers and mortality, there is correct (advanced) way to model this relationship. If this is not done, the model’s results are distorted (the independent variable is mis-specified). No amount of meta-analyses can correct that and simply combining studies with different referent ranges or different specifications of the independent variable in a meta-analysis is much worse statistically than requiring more stringent, homogeneous studies (as we have done) to analyze the effect of the biomarkers on mortality.

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.

The two points are excellent and we have revised the paper accordingly.

We would like to thank the reviewer for providing us with such insightful comments that have strengthened our manuscript.

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