Reviewer's report

Title: Cardiovascular Disease Relates to Intestinal Uptake of p-Cresol in Patients with Chronic Kidney Disease

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Reviewer: Tariq Shafi

Reviewer's report:

This is an interesting study by Poesen et al describing the association between 24 hour urinary excretion of p-cresol sulfate as a measure of intestinal uptake of p-cresol and the risk of first cardiovascular event in a non-dialysis CKD cohort. The paper is well written and easy to follow. My main criticism of the paper is in terms of the statistical modeling for longitudinal outcomes. I understand the authors’ desire to limit multivariate adjustment due to the small number of events but that leaves the study open to uncontrolled confounding.

Major Compulsory Revisions

1) Multivariate Cox proportional hazards regression models:

1a) Please identify the minimum set of variable that you will consider to be confounders a priori. In my opinion, these include age, diabetes, protein intake and eGFR. Other variables to consider: proteinuria, BMI, prevalent CVD.

1b) Consider sequential models with addition of these variables in the above order. Check to see if the addition of the model improves model fit of nested models.

1c) Is there a time-interaction that is being modeled? It is mentioned in methods and there seems to be a time interaction between the highest tertile and other tertiles based on the KM plot (at ~21 months). Please consider stratifying by time <18 months and >18 months.

1d) Table 3 and 4 with trivariate models are confusing – if you choose this approach then consider reporting all possible trivariate combinations – however, I would much rather see the sequential models as described in 1a above.

1e) Consider sensitivity analyses with tertiles of p-cresol sulfate with the lowest tertile as reference.

2) Is there information on prevalent gastrointestinal disease and antibiotic use available at baseline?

3) Discussion: It is difficult to conclude an “independent” association particularly due to the small number of events. Just association will suffice. Also, are the first CVD events truly “new-onset” as 26.5% of the cohort had prevalent CVD.

4) Discussion 4th paragraph: Another explanation for difference between the study by Wu et al and this study may be cultural and dietary differences and
should be discussed.

5) Discussion: I would like to see a paragraph describing the synthesis, absorption, metabolism and excretion of p cresol. It does not have to be detailed but should succinctly describe what is known and what is unknown. This paragraph could then be followed by a description of the factors describing inter-individual variability.

6) Discussion: Please discuss the negative studies of the association between serum p-cresol sulfate and outcomes and if your study helps explain these prior studies.

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

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:** None