Reviewer's report

**Title**: Chronic Kidney Disease of uncertain aetiology; prevalence and causative factors in a developing country

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**Reviewer**: Giuseppe Remuzzi

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The manuscript by Jayatilake and coworkers describes an apparently new form of chronic kidney disease which cannot be attributed to diabetes, hypertension, or other known etiologies that has emerged in some regions of Sri Lanka.

The following drawbacks are for the Authors’ consideration:

1. A lot of literature has been already published in the past on the topic of this peculiar chronic renal disease in Sri Lanka. Thus in the background of the manuscript the Authors should briefly mention the state-of-the-art about prevalence and etiology of the disease. This will help the readers to appreciate the novelty of the present paper, that, by the way, should be clearly presented in this section.

2. Criteria for case definition of chronic kidney disease of uncertain etiology (CKDu) as well as the paragraph about how this population prevalence study was conducted are now reported in the Background Section (page 4-5). They should be more appropriate for Methods and should be moved in this section of the manuscript.

3. To grade CKDu, beside albuminuria they have considered estimated GFR (eGFR) using the 4-variable MDRD. They may be aware of the new CKD-EPI equation to estimate GFR, that apparently provides better performance than MDRD, especially for CKD stage 1 and 2 (AS Levey, Intern Med 150:604, 2009), and eventually a more suitable classification of screened population. Thus, the Authors should analyze their data according to the CKD-EPI formula. Moreover, the term “grade” for CKD should be changed into “stage”.

4. Body weight was measured using a calibrated weighing scale to the nearest 0.1 kg. More information about weight measurement are required, including whether the procedure was performed with or without garments.

5. A key element of the study is to dissect possible etiologies for CKDu. To this purpose they have planned to analyze cadmium, arsenic, and lead in urine, blood, hair, and nails. It is unclear, however, why this analysis was not performed in all 733 individuals diagnosed with CKDu in the three districts in the endemic area. For example, as for urine analysis, the evaluation was performed only in randomly selected 495 cases. Does this shortcoming contribute to less robust conclusion?
6. Results are intriguing, reporting in page 9 higher prevalence of CKDu in females than males, with the latter accounting for higher rate of progression to CKD stage 3-4. This is an interesting observation that needs to be adequately addressed in the Discussion session, by providing a suitable explanation for this discrepancy, and comparing the findings with those previously published in the literature.

7. On the basis of their findings the Author hypothesize that chronic exposure to low levels of cadmium as well as low serum selenium, a metal that protect the kidney from oxidative stress, may be causative factors of CKDu in Sri Lanka. However, by ROC analysis they should define the threshold of urinary cadmium concentration and serum selenium levels that anticipate higher risk CKDu in the study population.

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

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

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

**Declaration of competing interests:**

I declare that I have no competing interests