Reviewer's report

Title: High Prevalence of Chronic Kidney Disease in Iran: a Large Population-Based Study

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Reviewer: Olafur Skuli Indridason

Reviewer's report:

High prevalence of CKD in Iran

1. Is the question posed by the authors well defined?
   yes

2. Are the methods appropriate and well described?
   Not entirely

3. Are the data sound?
   yes

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   No

5. Are the discussion and conclusions well balanced and adequately supported by the data?
   Yes but there needs to be a lot more discussion of other factors

6. Are limitations of the work clearly stated?
   No

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
   yes

8. Do the title and abstract accurately convey what has been found?
   To most degree

9. Is the writing acceptable?
   No, English needs to be addressed.

But mostly see below:

This study describes the prevalence of CKD in Iran based on eGFR calculated by the MDRD equation. This is worthy of publication based on the fact that we do not have much data from this part of the world. However, there are severe limitations that need to be
addressed.

Major

Creatinine is measured by a Jaffe reaction and the results are not standardized to the current standard of IDMS. While I see this as a major problem, it may only require a better description of the method itself and official reference range for this measurements, as well as discussion of the limitation it encompasses. Neither is done in this manuscript but it would help those that read it in estimating the bias in the estimate of prevalence of CKD in the population, as it is certainly high. If the reference range is higher than one expects (perhaps 70-120 mcmol/l as in some of the Jaffe reaction methods), the MDRD study equation will underestimate the eGFR (as the eGFR is lower if serum creatinine is higher) and overestimate the prevalence of CKD. This needs to be addressed in the discussion. It would be preferable that all serum creatinine measurements in the world were performed using a method standardized to the IDMS (Isotope dilution mass spectrometry) method but we do not have that possibility yet.

Other, some major.

Few studies (and not the one referenced) have shown an increase in CKD in general, however there has been an explosion of ESRD patients in the world as the reference they use clearly shows. This needs to be clarified.

The definition of diabetes does not include a measurement of a post-glucose load blood glucose as there is no mention of such a measurement in the method section. This needs to be clarified.

There is a considerable difference in the male:female ratio which is similar to what has been observed in other studies. This needs to be discussed in that context and the possibility of overestimation of CKD by the equations. Also the male:female ratio f ESRD in Iran should be mentioned in this regard as in most societies there are more men than women (55-60/45-40) entering ESRD registries. It would be informative to have this information to look to in this article. This needs to be discussed in the context of ESRD in Iran and male:female ration in Iran (see below)

It is of interest that all measures of body size are related to CKD. To my knowledge there is no evidence that overweight persons (controlled for diabetes and high blood pressure) enter dialysis more frequently than the lighter ones (correct me if I am wrong). This also needs to be discussed in the context of ESRD in Iran, are all dialysis patients fat? On the same note, smokers (who generally are lighter and younger than non-smokers) are less likely than non-smokers to have CKD. I wonder if body size (and therefore muscle mass) is therefore the most important predictor of serum creatinine and therefore the eGFR.

Individual sections:

Abstract:
In the discussion there needs to be more discussion of the limitations of the assay and the equation used.

Background, page 3:
First paragraph, first sentence. I believe it is difficult to show data for increasing prevalence of CKD but the reference they use certainly shows an increase in the prevalence and incidence of ESRD, reference 11 in the manuscript might serve to indicate an increase in the prevalence of CKD though.

First paragraph, second and third sentences (ref 3 and 4) there is an certain repetition here and I think there should be an condensation here.

Page 4.
“……are outcomes of exposure to ....” I do not understand this part, perhaps they want to say that CKD itself is a risk factor for cardiovascular disease but this needs to be clarified.

Methods.
The authors describe an elaborate selection process based on households in a Teheran district (District 13). We need to know how the population in this district compares to the rest of the nation and then how those participating in the study compare to those who did not with regard to age (the study sample is relatively young), gender (58% are women but in most countries this is close to 50:50 (knowing some of the gender policies in Iran this may be an issue but there also might be a shortage of men)), race (the MDRD equation incorporates African Americans or black race), presence of treated diabetes and possibly height, weight or BMI or smoking

Page 5
They say that all blood biochemical analyses were performed at the TLGS laboratory on the day of blood collection. Analyses were performed using the Selectra 2 autoanalyser (Vita.......... from the Netherlands........) but then they say that plasma glucose was assayed with an other method and cholesterol with ......This needs to be clarified. In particular, the description of the creatinine assay needs to be described in far more details and how the chosen method compares to other standard methods.

Page 6. no mention is made of subjects taking lipid lowering medications.
DM was defined by a method not used, i.e, a 2 hour post load serum glucose but in the method section you only describe a fasting sample.

Results.
Please consider along with the overall numbers, to report separately serum creatinine and eGFR form men and women.

The age adjusted prevalence is far lower than the prevalence in the cohort (15 vs 19%). Yet, you say that the study sample is young. We need to know the
difference between the study sample and the general population in Iran (see point 1 under Methods). + your study examines persons > 20 years of age which is lower than most studies.

Discussion.
The study shows a remarkable high prevalence of CKD in Iran. Yet the discussion fails to address the most likely cause for this observation, i.e. the difference in the creatinine assay used here and in other studies. It actually also fails to point out clearly the fact that these prevalence numbers actually are similar to some other nations (and the possible explanations for this (again the assay issues come in strong as well as possible issues with population differences). Moreover, they claim that the muscle mass of Asians and Iranians is lower, and the ingestion of meat is lower than in other ethnic groups. This should lead to lower serum creatinine levels and therefore lower eGFR. Their argument that this might lead do higher prevalence of CKD therefore does not seem plausible. I

The analysis of factors associated with the presence of CKD is interesting an mostly because any measure of body size, age or gender are significant, even though some of these variables are incorporated in the MDRD equation (although not any measure of body size). I do think that this deserves some more discussion of the problems with the equations. While I do not have statistics for Iran, in most western countries, men outnumber women in ESRD. Men also are more likely to develop cardiovascular disease. The males:female issue in CKD therefore does not make sense and has nor been addressed adequately in any paper that I know of. Indeed, I suggest the authors redo their statistics for the genders separately.

Obvious problems of not estimating CKD in general due to lack of information on proteinuria and other kidney and urinary abnormalities can be brushed off by its lack in many other studies.

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.