Reviewer's report

Title: Chronic kidney disease among high school students of Kinshasa, the Democratic Republic of Congo.

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Reviewer: Jeffrey Fadrowski

Reviewer's report:

Thank you for the opportunity to review this interesting manuscript. Epidemiologic studies regarding kidney disease in Africa are lacking, so this manuscript is of great interest.

Major compulsory revisions

1. The comparison of original Schwartz equation and MDRD to Cockcroft-Gault is not valid as the first two equations are adjusted for body surface area, and the CG is not. Normalization to body surface area (1.73 m²) increases the accuracy of CG, and this is recommended (and required in the case of your study if you wish to compare equations). The discrepancy you observe with CG compared to other two equations is likely largely related to failure to adjust to body surface area. The CKD stage definitions use units of mL/min/1.73m² (not mL/min). Furthermore, the CG requires multiplication by 0.85 in women to account for smaller muscle mass compared to men.

2. The accuracy of GFR estimating equations is known to be highly dependent on creatinine assay. Your center is using Jaffe method, which is similar to method used in the equations you chose to evaluate, and this is appropriate. However, as many centers move towards enzymatic creatinines (resulting in lower creatinine results), and given efforts of National Kidney Disease Education Project (NKDEP) to standardize creatinine measurements internationally, these equations will not be appropriate. The Schwartz equation in particular is known to overestimate GFR by >20-30% when used with enzymatic creatinines. The recently developed CKiD equation for kids and CKD-EPI equation for adults (>18 years) utilize creatinines determined by/standardized to enzymatic methods.

• You do not need to provide a “review” of methods of estimation of GFR in your paper, but if you are using these results to estimate prevalence of CKD in the DRC, you should better inform the reader why you chose the equations you did (presumably as your hospital is still using Jaffe creatinine assay, which best matches creatinine assay used by Schwartz, MDRD, CG).

○ The “revised” Schwartz equation (reference 23) you mention does not require cystatin C/urea. The paper you reference uses the “bedside” Schwartz/CKiD formula, which only uses creatinine (as opposed to complete revised Schwartz/CKiD). Furthermore, if referencing the new Schwartz/CKiD equation, the original article should be referenced: Schwartz, GJ, et al. “New equations to estimate GFR in children with CKD”. JASN 2009. However, given the use of the
Jaffe method at your center, I agree with your choice not to use revised Schwartz/CKiD formula.

- GFR estimating equations (MDRD has most literature supporting; poorly studied for Schwartz) are known to underestimate GFR, especially at higher levels of GFR (your population). This was the impetus for the development of CKD-EPI equation...to improve accuracy of estimation at higher levels of GFR. This limitation must be acknowledged given the aim of your study to estimate prevalence of CKD. Given potential for GFR underestimation with these equations, your estimates of CKD may be inflated. Furthermore, you should acknowledge that accuracy of given equation may be limited by lack of validation in certain age groups (for example, Schwartz not intended for >18 years, and MDRD not developed for/evaluated in persons <18 years).

3. You appropriately mention the limitations regarding proteinuria assessment in your analysis, including the likelihood of orthostatic proteinuria. Orthostatic proteinuria can still not be ruled out by a 24 hour urine collection in adolescents, unless the collection is fractionated. The older participants in your study may be less likely to have orthostatic proteinuria. It would be interesting to know the ages of the children with proteinuria on the 24 hour urine collection. Given that proteinuria seems to be driving most of the CKD prevalence in your study (and the proteinuria assessment is limited), and as you acknowledge that the diagnosis of CKD requires 3 months of evidence of sustained kidney damage, you should soften your statements about the prevalence of CKD in the DRC. For example, the first sentence of your Conclusion might better read, “This study estimates that roughly 2% of students have proteinuria and/or estimated GFR <60 in Kinshasa, supporting a possible diagnosis of CKD.” You have not established the diagnosis of “CKD”.

4. Given above limitations, the true prevalence of CKD is likely <2%, and likely <1%. Given this prevalence, do you think systematic urinalysis/creatinine/imaging is warranted and/or cost-effective? This should be considered in light of “false positive” screening results as well (for example, 7.4% of participants dipstick positive proteinuria, 1% with significant proteinuria on 24 hour collection, and fraction of these may have orthostatic proteinuria). Studies exist that estimate cost-effectiveness of urine dipstick screening based on prevalence of CKD in the population that could help inform your decision. In, the US, such studies have contributed to the recommendation against dipstick screening in children. Thus, a prevalence study such as yours is quite important in determining the need for CKD screening. The need for screening is your opinion, of course, but I would justify it based on previous study and available resources. Another option might be to repeat the study in a larger cohort, with 1st AM urine collections, etc, to confirm burden of CKD.

5. You should be careful with the label of “Hypertension”. Although the method of blood pressure measurement was ideal, and 3 values obtained, the definition requires elevated blood pressures on 3 separate occasions. Most studies have shown that with successive BP measurements in same subjects, prevalence of hypertension decreases. Thus, “elevated blood pressure” or “hypertensive blood
“pressure” would be more accurate (unless the child is actually taking hypertension meds, the prevalence of which you don’t describe).

6. I’m not clear on the usefulness of Table 3. Why is only the Schwartz formula presented, when an aim of this paper is to compare various estimating equations in this age group? Consider placing the creatinine values in Table 1. Then consider using Schwartz, MDRD, and CG (not stratified by gender) as the column headers. If the intent was to explore differences by gender, I think this is sufficiently covered by reporting creatinine in Table 1 (estimated GFR doesn’t add to this analysis). The higher creatinine observed in females is puzzling (and I don’t think fully explained by slightly higher BMI, as BMI is likely driven mainly by fat, and not muscle, and thus should not contribute to higher creatinine unless accompanied by some other morbidity [diabetes] which seems unlikely with this BMI range). You addressed these unexpected results in the Discussion, and I don’t think more explanation can be provided given the limitations of your data.

Minor Essential Revisions

1. Decimal point missing in SD, Table 1, Males, BMI, kg/m2.
2. It is not clear if the patients with GFR<60 had higher (hypertensive) blood pressure and/or proteinuria. Given small sample size, would be worth describing. IE, could these children be identified by blood pressure? Would this be a more effective way to determine if further testing needed (dipstick, creatinine, etc)?
3. Discussion: (hematuria) Is there an advantage to early detection of IgA nephropathy or thin basement membrane nephropathy in the absence of proteinuria? IE, would you treat this? Would proliferative glomerulonephritis be expected to present with no proteinuria?
4. “Hence, in the present survey dealing with younger subjects, in the absence of a reference test, we believe that the MDRD study should be used as a surrogate of Schwartz formula in the estimation of GFR”. Why disregard a formula developed in and for the pediatric age group, based on this study showing reasonable agreement with MDRD, but with small sample size and no comparison to gold-standard GFR measurement? Is it because height (Schwartz) is difficult to obtain when screening with creatinine? Further rationale need for this statement.
5. Although generally well written, attention will need to be paid to organization/flow of manuscript, and some grammar/phrasing issues (best addressed by editorial board).

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

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

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

I declare that I have no competing interests.