Author’s response to reviews

Title: Revisiting Racial Differences in ESRD due to ADPKD in the United States

Authors:

Erin Murphy (erin.l.murphy@yale.edu)
Feng Dai (feng.dai@yale.edu)
Katrina Blount (katrina.blount@yale.edu)
Madeline Droher (madeline.drohere@yale.edu)
Lauren Liberti (lauren.liberti@yale.edu)
Deidra Crews (dcrews1@jhmi.edu)
Neera Dahl (neera.dahl@yale.edu)

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Author’s response to reviews:

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Dear Dr., Mekahli,

Thank you for the opportunity to revise our manuscript.

We have made the corrections and some clarifying comments to each of the reviewers’ comments below.

1. Our largest concern regards the associational nature of the study and that one has to be very careful to interpret its results. The authors do a nice job of mentioning some of these issues during the limitations section but these issues should be emphasized elsewhere in the manuscript to avoid the reader over-interpreting the results. As the authors mention in the limitations, the earlier onset of ESRD in non-Hispanic blacks has many different potential explanations, including possible differential rates of pre-emptive transplantation in whites versus blacks. This explanation alone may be source of the differences seen and we feel this point deserves emphasis in other sections of the manuscript, particularly in the discussion and abstract.
We have changed incident ESRD attributed to ADPKD to ...initiated dialysis in the abstract and moved up a discussion of limitations to the discussion section. Although we agree that there is a discrepancy with percentage of whites vs blacks being transplanted we would expect this to increase the number of blacks vs whites who initiate dialysis with ESRD and this was not seen.

2. Additionally, the authors nicely describe the several other potential explanations of their data including socio-economic differences across races, differences in use of renal imaging modalities in whites versus blacks, as well as potential other comorbidities such as hypertension, diabetes but also importantly sickle cell trait/disease and APOL1 risk alleles. We feel that this information needs to be stated explicitly in the abstract, and that the sentence "Until further data are available, it may be prudent to consider black race an additional risk factor for progression in ADPKD" (page 2, lines 26-28) should be stricken from the manuscript, as it is too strong of a conclusion given these limitations in the data.

With respect, we have revised rather than removed this sentence. The BMC Nephrology guidelines state that the abstract conclusions contain a brief summary and potential implications. We believe that consideration of race in progression of ADPKD is a potential implication of this work. To highlight that this is an implication and not a conclusion the new sentence now reads: A potential implication of these findings may be that black race should be considered as an additional risk factor for progression in ADPKD.

3. Are the authors familiar with any data on differential rates of the different PKD mutations by race? We suspect this has not been studied given the relatively homogenous populations involved in the groups from which risk calculators were derived. If data does not exist, it would be worth emphasizing that this is an important area of future study. Related to this, we might suggest the word "expectation" in the last paragraph of the Introduction be changed to "assumption", as this may not be valid.

We have changed expectation to assumption. We are not aware of any data looking at PKD mutations by race. The last line of the paper suggests that further studies are needed.

4. A lot of the conclusions vary based on what is entered as the primary diagnosis for ESRD on the 2728 form. Do the authors know of studies that have supported the reliability/accuracy of ADPKD being reported as the primary diagnosis (as compared with secondary diagnoses)? Also
there is no option to enter 753.12, which is sometimes uses as a PKD diagnosis. This would obviously affect things greatly if there is evidence that nephrologists enter ADPKD as a later diagnosis following HTN or DM, or others.

The 2728 form only allows for a primary diagnosis of ESRD, so it’s possible that we’d have a better data set if secondary diagnoses were also permitted.

5. We were surprised with the degree to which the decrease in ESRD secondary to ADPKD after adjusting for the stratification factor of year was lower in blacks (OR 0.38) when compared with other analyses such as the lower incidence of ESRD of 0.864 vs. 0.912 per 100,000. This was also dramatically different from the similar analyses after adjustment for year in the group with DM (OR 0.95). Can the authors explain this? It may require more clarity in the methods.

The stratification results were calculated with the use of same method as for all outcomes and dramatical differences were because of the different distributions of outcomes in black vs. white.

The rate of ESRD secondary to ADPKD was consistently much lower (less than 0.5 times) in blacks compared to White from 2004-2013 (Figure 2 A). The OR estimates (black vs. white) at each year were statistically non-different (as judged by overlapping 95% confidence intervals, in attached figure) either among each other, or compared to the year-adjusted overall value. Please see a figure demonstrating these results for ADPKD in the uploaded response to reviewers as I could not paste the figure here.

6. We don't understand the variability shown in Figure 2B. The denominator (population) doesn't change. Please clarify.

The total US population number at each year was different. So, the denominator varied at different years.

Overall, we feel that the strength of the conclusions with regard to non-Hispanic black having more rapid progression to ESRD be dampened considerably as they likely are much stronger statements as currently written than the results justify.
As noted above, we have labeled this a potential implication of the work.

Reviewer #2: I read with interest the paper by Murphy EL, et al. First of all, there are discrepancies between text and Figures: In text, a higher incidence of ESRD secondary to diabetes in non-Hispanic black patients compared to non-Hispanic white patients is mentioned, whereas, the opposite is represented in Figure 1. A similar discrepancy is observed concerning the incidence of ESRD secondary to HTN. This questions the interpretability of the data.

The tables and figures are correct. In Table 1, the incidence of ADPKD is given in relationship to the total number of Blacks or Whites for the diagnosis. This data is adjusted for the numbers of blacks and whites in the population using the US Census data, as noted. In Figure 1 the total number of incident ESRD is given. Since there are more whites in the population than blacks the DM, white is the highest incidence.

Furthermore, in the introduction, the authors claims that "the incidence of ADPKD is equal between races".

We have changed the word expectation to assumption in the introduction as also suggested by reviewer 1.

Still, according to Reference 1 (Levy M, et al. Kidney Int. 2000; 58(3): 925-943.), the incidence of ADPKD may actually differ between races. Such a putatively lower prevalence of ADPKD in black patients is also suggested in Yium J, et al. J Am Soc Nephrol. 1994;4(9):1670-1674. These previously reported observations may significantly impact on the interpretation of the authors' results, and, therefore, should be taken into account in a more balanced interpretation.

We agree that there is discrepancy in the previously reported studies about the impact of race in ADPKD and reviewed those older findings in our introduction. The Yium paper is reviewed in the introduction, and is reference 10 in the paper.

The legend of Table 1 is confusing: "Average 10-year incidence of ESRD for each primary diagnosis in non-Hispanic Black and non-Hispanic white patient populations." Since the
denominator is "numbers from the US Census", it should say "Average 10-year incidence of ESRD for each primary diagnosis in non-Hispanic Black and non-Hispanic white general population".

We have amended the legend for Table 1 to read: Average (95% CI) 10-year incidence (N per 100,000) of ESRD for each primary diagnosis in the general non-Hispanic Black and non-Hispanic White populations.

Please correct or justify why you use the term "patients".

We have removed the word patient from all the legends and from the discussion in the text.

Thank you for your consideration of this revised manuscript.

Sincerely,

Neera Dahl