ARIC Manuscript Proposal # 3062

PC Reviewed: 11/14/2017  Status: _____  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

1.a. Full Title: Matched Comparison of eGFR Trajectories of Living Kidney Donors (WHOLE-Donor) versus Non-donors (ARIC)

   b. Abbreviated Title (Length 26 characters): Matched LKD eGFR trajectories

2. Writing Group:
   Writing group members: Courtenay Holscher, Dorry Segev, Jacqueline Garonzik Wang, Allan Massie, Josef Coresh, Morgan Grams, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __CMH___ [please confirm with your initials electronically or in writing]

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3. Timeline: Matching and analysis done by summer 2018, anticipating submission of results as conference abstract by fall 2018 with manuscript to be written before 2019.

4. Rationale:
   At cross-sectional follow-up, approximately 14% of living kidney donors have a post-donation eGFR <60mL/min/1.73m² which is sufficient to diagnose stage 3 chronic kidney disease,
however it is unclear what the meaning of a CKD diagnosis is in living kidney donors nor the specific trajectory of how they arrived at the lower eGFR. In the general population, CKD diagnosis is associated with progression to ESRD, cardiovascular events, and death. It is not clear that these outcomes or further eGFR decline should be expected in kidney donors overall or those with eGFR<60mL/min/1.73m². We propose a matched analysis of eGFR trajectories of donors and comparably healthy non-donors using two prospective cohorts with rich demographic and clinical data: the Wellness and Health Outcomes of LivE Kidney Donors (WHOLE Donor) study and the Atherosclerosis Risk in Communities (ARIC) study. Understanding differences between donor and non-donor eGFR trajectories will improve our understanding of the risks of decline in kidney function in donors.

5. **Main Hypothesis/Study Questions**: What does the exposure of living kidney donation do to eGFR trajectory within various subgroups?

6. **Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).**

**Study population**

Donors enrolled in the WHOLE-Donor study will be matched with non-donors enrolled in the ARIC study. WHOLE is a cohort of living kidney donors at least two years post-nephrectomy who donated up to 30 years ago. Subjects participate in a series of surveys and their medical records are abstracted from primary care, specialty care, and hospitalizations they have had. As such, this ongoing study is compiling a rich database of long-term clinical data on living kidney donors. At this point, we have 795 donors with both pre-nephrectomy creatinine and at least 3 post-donation serum creatinine values abstracted from medical records, with data collection ongoing. WHOLE subjects are representative of the composition of US living kidney donors, with the majority white, female, and middle-aged at time of donation. Though there will be donors in WHOLE who cannot be matched to the ARIC participants (who are age 45-64 years at enrollment) due to ages outside this range at the time of donation, this cohort of US donors is already the largest with long-term clinical data available.

**Matching**

We will explore matching on key CKD progression risk factors (baseline age, race, sex, BMI, eGFR before donation/at ARIC enrollment, blood pressure, and usually absent in donors - history of diabetes and CVD). In addition, we will explore propensity matching on additional variables depending on differences which may be present between the two cohorts. In particular, proteinuria is important but often missing in our donor database and only present in ARIC starting at visit 4, thus we may have to restrict to subjects with data available, with imputation for sensitivity analyses. We could also consider excluding ARIC control subjects who had significant proteinuria identified at visit 4.

**Exposures of interest**
Exposures of interest include donor nephrectomy, age, race, sex, BMI, initial/post-donation eGFR, initial/post-donation proteinuria, initial/post-donation SBP, smoking history, and family history of ESRD/donor biologically related to recipient.

Outcomes of interest
The outcome of interest is eGFR trajectory.

Statistical analysis
This matched prospective cohort study will use longitudinal data analysis per prior published methods analyzing GFR in general and in ARIC specifically [Grams JASN 2016]. Linear mixed effects models will be used with clustering by participant to allow for individual slopes and intercepts. In secondary analyses, if supported by data available, matched survival analysis will be used for the outcome of CKD development defined as eGFR<60mL/min/1.73m².

Limitations
There are several limitations to this study. First, the study populations are different. ARIC recruited a general public population and includes only those age 45-64 at enrollment. WHOLE includes those healthy enough to donate a kidney and a broader age range. Matching on baseline characteristics will help control for differences in these study populations, but might limit the number of donors able to be matched. Next, WHOLE is an ongoing study and might have limited follow up data available. Differences in data collection between WHOLE which largely relies on clinical data and ARIC’s research protocol measures limit inferences in any between cohort comparison such as this one. However, WHOLE has the largest US cohort of donors with long-term clinical data available. Finally, there is evidence that in individuals with CKD, many patients have a non-linear eGFR decline or a non-progression period. By including a large matched study population with long-term clinical data available, we hope to mitigate this limitation.

7.a. Will the data be used for non-CVD analysis in this manuscript? _____ Yes    ____ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? _____ Yes    ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? _____ Yes    ____ No

b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”? _____ Yes    ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.
ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

___x___ Yes    _______ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?


11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ___ Yes    ___X__ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* __________)
___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PubMed Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes    ___X__ No.