

## ARIC Manuscript Proposal # 3386

PC Reviewed: 5/14/19  
SC Reviewed: \_\_\_\_\_

Status: \_\_\_\_\_  
Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

**1.a. Full Title:** Association between physical activity and kidney function: The Atherosclerosis Risk in Communities Study

**b. Abbreviated Title (Length 26 characters):** Physical activity and CKD

### 2. Writing Group:

Writing group members: Shoshana Ballew, Josef Coresh, Morgan Grams, Kaushik Parvathaneni, Casey Rebholz, Elizabeth Selvin, **others welcome**

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

### First author:

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**ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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### 3. Timeline:

Analysis will begin upon receipt of the data and approval of the manuscript proposal. Manuscript will be written and submitted for ARIC Publications Committee review within one year of manuscript proposal approval.

### 4. Rationale:

Chronic kidney disease (CKD) represents a significant public health burden, affecting an estimated 11% to 13% of the population worldwide, and is expected to increase in prevalence.<sup>1</sup> Identifying modifiable lifestyle factors that have protective benefits on the kidney can help guide disease prevention efforts. Physical activity is one such factor that has been shown to reduce the risk of chronic illnesses such as cardiovascular disease, diabetes, and cancer.<sup>2</sup> However, its relationship with kidney disease is not as well understood.

While several cross-sectional analyses suggest physical activity is associated with improved renal function prospective studies are limited and report contradictory findings.<sup>3,4,5</sup> A recent analysis of the Doetinchem Cohort Study concluded there is no relationship between physical activity and kidney function, as measured by estimated glomerular filtration rate (eGFR).<sup>6</sup> Additionally, an analysis of the Framingham Heart Study failed to show an association between physical activity and incident eGFR decline  $< 60$  ml/min per  $1.73$  m<sup>2</sup>.<sup>7</sup> However, two other prospective studies demonstrated a statistically significant protective benefit of physical activity against development of chronic kidney disease and incident rapid eGFR decline.<sup>8,9</sup> Interestingly, despite agreeing on the direction of the signal, there is marked variation in the magnitude of the associations reported between the two studies. Further study of the effect of physical activity on kidney function is warranted.

We aim to help resolve such discrepancies in the literature by prospectively examining the association between physical activity and incident CKD and end stage renal disease (ESRD) in adults enrolled in the Atherosclerosis Risk in Communities (ARIC) study.

#### **5. Main Hypothesis/Study Questions:**

Evaluate the association of physical activity with the development of CKD in healthy adults. We hypothesize that greater physical activity is associated with reduction in incident CKD, independent of covariates.

#### **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 Design:**

We will conduct a prospective analysis of the ARIC cohort, using study visit 1 (1987 – 1989) as baseline with follow up through December 31<sup>st</sup> 2017.

##### **Study Population:**

The study population will include all members of the ARIC cohort that have available physical activity data and creatinine measurements at visit 1. Individuals will be excluded if they are missing follow up information on CKD or ESRD outcomes. We will also exclude those with eGFR  $< 60$  ml/min per  $1.73$  m<sup>2</sup> at baseline.

##### **Exposure:**

Physical activity as measured by an interviewer administered modified Baecke Physical Activity Questionnaire at visit 1 and visit 3. The reliability and validity of the Baecke Questionnaire has been previously reported.<sup>10,11</sup> The questionnaire asks about type, duration, and frequency of participation in up to four sport activities during the past year. At visit 1 and at visit 3, each activity will be converted into a metabolic equivalent (MET) ranging from 1 to 12 based on intensity in accordance with the Compendium of Physical Activities.<sup>12</sup> We will combine the duration, frequency and MET of all activities at each visit in order to generate a multiplicative term, MET\*min/week. We will use the average MET\*min/week of visit 1 and visit 3 for our continuous variable model. For our categorical analysis we will create distribution based quintiles of average MET\*min/week values. For those participants who lack data on physical

activity at visit 3 or for those who experienced a CKD event prior to visit 3, we will use physical activity data as assessed at visit 1 only.

We will also look at categorizing METs using the American Heart Association (AHA) physical activity guidelines. Moderate exercise is defined as 3 – 5.9 METs and vigorous is  $\geq 6$  METs.<sup>12</sup> These will be subsequently combined with duration and frequency to generate AHA based categories: as recommended ( $\geq 75$  min/week of vigorous intensity or  $\geq 150$  min/week of any combination of moderate and vigorous intensity), intermediate (1 – 74 min/week of vigorous intensity or 1 – 149 min/week of any combination of moderate and vigorous intensity), or poor (0 min/week of moderate or vigorous intensity).<sup>13</sup> This classification is consistent with the 2018 Physical Activity Guidelines for Americans.<sup>14</sup>

### **Outcomes:**

The main outcome is incident chronic kidney disease. The eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation incorporating serum creatinine values.<sup>15</sup> The eGFR will be measured at visits 1, 2, 4, 5, and 6. In sensitivity analysis, eGFR will be calculated using cystatin C because cystatin C is less affected by changes muscle mass associated with physical activity or older age compared to creatinine.<sup>16</sup> Incident chronic kidney disease will be defined as meeting any of the following criteria: 1) eGFR  $<60$  ml/min per  $1.73 \text{ m}^2$  at follow up and at least 25% decline in eGFR relative to baseline 2) CKD-related hospitalization or death based on ICD-9 or ICD-10 codes 3) incident ESRD as defined below.<sup>17</sup>

The secondary outcome is incident ESRD. Incident ESRD will be defined as the initiation of dialysis therapy or transplantation as identified by the United States Renal Data System (USRDS) registry. In sensitivity analysis, we will use a composite outcome of kidney failure defined as 1) ESRD 2) eGFR  $< 15$  ml/min per  $1.73 \text{ m}^2$  at follow up 3) ICD-9 or ICD-10 code for a kidney failure related hospitalization or death.<sup>18</sup>

### **Statistical Analysis:**

Descriptive statistics will be used to examine baseline characteristics of the study participants according to quintiles of physical activity. Differences will be tested using chi square test for categorical variables and linear regression for continuous variables.

Cox proportional hazards regression will be used to estimate the association (hazard ratios, 95% confidence intervals) between physical activity quintile and risk of CKD, incorporating time to the development of kidney disease and accounting for censoring. Restricted cubic splines will be used to perform a continuous analysis using the MET\*min/week variable.

Potential covariates for multivariable regression models include: age, sex, race, body mass index, DASH diet score, alcohol, cholesterol, systolic blood pressure, anti-hypertensive medication use, diabetes status, cardiovascular disease status, smoking status, and socioeconomic status.

We will test for interactions between physical activity and sex, as well as physical activity and diabetes and hypertension.

**Limitations:**

This is an observational study so we cannot make causal inferences and there is the possibility of residual confounding. Physical activity is self-reported rather than objectively measured so there may be recall error.

**7.a. Will the data be used for non-CVD analysis in this manuscript?** \_\_\_ Yes \_\_\_X\_\_\_ 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 \_\_\_X\_\_\_ No

**8.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.csc.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)?**

None

**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.csc.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.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](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](mailto:pingping_wu@unc.edu). I will be using CMS data in my manuscript \_\_\_\_ Yes  No.

## References

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