

**ARIC Manuscript Proposal #3052**

**PC Reviewed:** 10/3/17  
**SC Reviewed:** \_\_\_\_\_

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

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

**1.a. Full Title:** CKD and Short-Term Risk of Hospitalization in Older Adults

**b. Abbreviated Title (Length 26 characters):** CKD & Hospitalizations

**2. Writing Group:**

Writing group members: Eugenia Wong, Shoshana Ballew, Natalie Daya, Junichi Ishigami, Kunihiro Matsushita, Morgan Grams, Josef Coresh. Others welcome.

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

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**3. Timeline:**

Data for the exposures and outcomes of interest has already been collected. Analysis to begin after approval of this proposal. An abstract will be prepared by October 2017 and a manuscript submitted for publication by April 2018.

#### 4. Rationale:

The overall prevalence of chronic kidney disease (CKD) in the US remains high and it has been estimated that nearly 15% of the population is affected by the condition.<sup>1</sup> Furthermore, the public health burden of CKD will likely be exacerbated by the country's aging populations. This notion has been supported by recent data from the National Health and Nutrition Examination Survey (NHANES 2011-2012) that demonstrated that approximately half of participants over the age of 80 had late-stage CKD.<sup>2</sup> However, considering that the CKD patient population is largely comprised of older individuals, there is a comparative dearth of research on this high-risk subgroup<sup>3-5</sup>; the number of studies of older age groups since the establishment of the most recent 2012 Kidney Disease Improving Global Outcomes (KDIGO) clinical guidelines is even more limited.<sup>6-8</sup> Furthermore, the majority of recent research on older CKD patients has focused on either disease progression, cardiovascular events, or mortality.<sup>9-13</sup> Less is known about the relationship between markers of CKD and rates of hospitalizations in this age group, although data has shown that hospitalizations in CKD patients occur most frequently in those over the age of 75.<sup>1, 14</sup> It has also been demonstrated that in a 5% sample of Medicare patients, the most common causes of hospitalization were cardiovascular disease and infection.<sup>1</sup> It would be of interest to examine whether these are also the most frequent causes of hospitalization in other population-based cohorts. Therefore, research that would further characterize the risks and types of hospitalizations in older CKD patients would add substantial value to the literature. The present study would address this scarcity of research through an investigation of the relationship between CKD prognosis and risk of all-cause hospitalizations among older adults.

There is evidence to suggest that the utility of estimated glomerular filtration rate based on serum creatinine (eGFRcr) in informing CKD prognosis may differ across age groups.<sup>15, 16</sup> The 2012 KDIGO clinical guidelines recommend the use of both eGFRcr and categories of albuminuria for initial assessment of CKD.<sup>17</sup> However, serum creatinine is dependent on muscle mass, which can lead to inaccurate measures of eGFR among those with very high or very low levels of muscle mass.<sup>18</sup> Consequently, categorizing risk with eGFRcr among older individuals, who may have extremely variable levels of muscle mass, may result in misclassification. Estimated glomerular filtration rate informed by another endogenous marker, serum cystatin C (eGFRcys), is an alternative indicator of kidney impairment and is currently recommended as a confirmatory measure to diagnose CKD.<sup>17</sup> eGFRcys is not correlated with muscle mass and multiple studies have recognized its potential as an improved predictor of prognosis among older populations.<sup>18-21</sup> Therefore, a study of the magnitudes of association between eGFRcr versus eGFRcys and risk of hospitalizations could serve as a useful comparison to inform whether one measure is a superior predictor of risk among older CKD patients.

As the target population of this study would be older patients affected by CKD, another factor of interest would be prevalence of frailty. Fried et al. were the first to establish a standardized definition of frailty, a clinical syndrome that is identified by the presence of at least three of five of the following characteristics: unintentional weight loss (10 lbs in the past year), self-reported exhaustion, weakness (as measured through grip strength), slow walking speed, and low physical activity.<sup>22</sup> It has been estimated that 15% of individuals over the age of 65 are frail and 45% of individuals of this same age group exhibit one to two frailty characteristics and are thus

considered “pre-frail”.<sup>23</sup> Evidently, it would also be useful to explore whether the relationship between eGFR, by either creatinine or cystatin C, and risk of hospitalizations is affected by frailty.

The Atherosclerosis Risk in Communities (ARIC) cohort is uniquely poised as a study that could explore all of the aforementioned topics pertaining to older CKD patients: the risk of all-cause hospitalizations, the value of eGFR<sub>cys</sub>, and the effect of frailty on eGFR based prognosis. At Visit 5 (2011-2013), the mean age of ARIC participants was 76, indicating that the age distribution of the cohort would be appropriate for the study of older CKD patients. Also, data on serum cystatin C was collected at Visit 5, and thus eGFR<sub>cys</sub>, in addition to eGFR<sub>cr</sub>, may be calculated for each participant. To explore hospitalization as an outcome, the ARIC cohort already has a hospital surveillance system in place that captures details, such as event type, length of stay, and discharge or death date. In conclusion, we propose to study CKD and risk of hospitalizations in the older adults of ARIC as the cohort is in many ways ideally positioned to explore our research aims.

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

**Aim 1:** Investigate the relationship between CKD categories (as indicated by measures of eGFR and albuminuria) and risk of hospitalizations among older patients.

**Hypothesis 1:** CKD categories (by eGFR and albuminuria) will be positively associated with overall risk of hospitalization among older patients.

**Aim 2:** Identify the types of hospitalizations that are most common among older CKD patients.

**Hypothesis 2:** CKD stages will be more strongly associated with hospitalizations for cardiovascular disease and infections in older individuals than other hospitalizations.

**Aim 3:** Evaluate and compare the association between eGFR<sub>cr</sub> vs eGFR<sub>cys</sub> and risk of hospitalization among older CKD patients overall and stratified by frailty status at baseline (ARIC visit 5).

**Hypothesis 3:** Among older adults, eGFR estimated by cystatin C will show a stronger and more linear association with risk of hospitalization - this will be particularly true among individuals with frailty where the prevalence of low GFR estimated by cystatin C will be much higher than the prevalence estimated by serum creatinine as seen in previous studies of this cohort.<sup>21</sup>

## **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:** Prospective cohort study beginning at ARIC Visit 5 (2011-2013).

**Inclusion/Exclusion:** Participants with baseline covariate data, serum creatinine, serum cystatin C, and albuminuria measures collected at Visit 5 will be included.

**Exposure:** Race, age, serum creatinine, and serum cystatin C values will be used to calculate both eGFR<sub>cr</sub> and eGFR<sub>cys</sub> in accordance with the CKD-EPI 2009 equation.<sup>24</sup> Albuminuria will be calculated as urine albumin-to-creatinine ratio (ACR). eGFR and ACR category will be used to diagnose and stage CKD based on current KDIGO guidelines.<sup>17</sup> The assessment of frailty will follow methods previously used by Kucharska-Newton et al. to operationalize the standard five-component definition of frailty in the ARIC cohort.<sup>25</sup>

Classification of frailty will be based on the fulfilment of at least 3 of the following characteristics:

Characteristic	ARIC Criteria
Weight Loss	10% of weight loss from V4 (1996-1999) to V5 (2011-2013) or BMI < 18.5 at Visit 5
Low physical activity	Gender-specific 20 <sup>th</sup> percentile rank of the Baecker leisure sports activity index
Slow walking speed	Gender- and height-adjusted time in seconds used to walk 4m, Slowest speed defined as the 20 <sup>th</sup> percentile of the distribution
Exhaustion	Responded “some of the time” or “most of the time” to the following questions: <i>I felt everything I did was an effort</i> or <i>I could not get “going”</i>
Low grip strength	Gender- and BMI-specific grip strength in the lowest 20 <sup>th</sup> percentile of distributions

**Outcome:** Counts of all post-Visit 5 hospitalizations captured by the ARIC hospitalization surveillance system, and all hospitalizations ascertained through annual telephone interviews, will serve as the main outcome. The first ICD-9 code listed by the event surveillance system will be used to classify hospitalizations by primary cause, and events will be further grouped into broad categories, such as malignancy, and infection as done previously by Schneider et al. in the ARIC cohort.<sup>26</sup>

Mortality will also be examined, given its importance and ultimate outcome as well as to examine its influence as a competing risk for hospitalization.

**Analysis:** As repeated measures in the form of hospitalization counts will be the primary outcome of the study, Poisson regression will be used to estimate incidence rates of all-cause hospitalization and their associated 95% confidence intervals for each stage of CKD. This will be done separately for GFR stages (G1 90+, G2 60-89, G3a 45-59, G3b+ <45 ml/min/1.73m<sup>2</sup>), albuminuria stages (A1 <30, A2 30-299 and A3 300+ mg/g) and risk groups defined by both albuminuria and GFR (low risk reference group [no CKD] – A1 and G1-G2 ; CKD with moderately increased risk – G3aA1 or G1-G2 A2; CKD with high risk G3bA1, G3aA1, G1-G2A3; CKD with very high risk G4+, G3bA2, G3aA3). Similarly, incidence rates of cause-specific hospitalizations will also be investigated. The strength of association between eGFR<sub>cr</sub> versus eGFR<sub>cys</sub> and hospitalizations will be evaluated through multivariable modelling of both eGFR<sub>cr</sub> and eGFR<sub>cys</sub> and cross-classification of eGFR categories. The analysis will be repeated stratified by frailty and an overall model will be used to test for dose-response relationships and

interactions of frailty with eGFR. We hypothesize that frailty will be associated with a larger under-estimate of the prevalence of CKD G3+ by eGFRcr compared to eGFRcys. Furthermore, the risk relationship between eGFR and risk of hospitalization and mortality will be U-shaped and blunted for eGFRcr but remain strong and more linear for eGFRcys. We will also evaluate the impact of obesity (at visit 5 and previous visits) on the CKD and hospitalization risk relationships. This is important as much of previous eGFR and risk relationship research (e.g. in the Cardiovascular Health Study) was completed prior to the current obesity epidemic. Mortality will be modeled similarly to hospitalization and its influence as a competing risk for hospitalization will be examined to appropriately model absolute risk of hospitalization as a function of CKD stage at older age.

**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

**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.c.unc.edu/ARIC/search.php>**

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)?**

**#1118:** Kidney Function as a Risk Factor for Heart Failure Hospitalization: The Atherosclerosis Risk in Communities (ARIC) Study

**#1348:** Chronic kidney disease and risk of hospitalization: The Atherosclerosis Risk in Communities Study

**#2624:** Chronic kidney disease and risk for infection in the community: The Atherosclerosis Risk in Communities (ARIC) Study

**#2919:** The association of kidney disease measures with physical function in older adults: The Atherosclerosis Risk in Communities (ARIC) Study

**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 \_\_\_x\_\_\_ No.

References:

1. System USRD. 2016 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. 2016.
2. Murphy D, McCulloch CE, Lin F, Banerjee T, Bragg-Gresham JL, Eberhardt MS, Morgenstern H, Pavkov ME, Saran R, Powe NR, Hsu CY, Centers for Disease C and Prevention Chronic Kidney Disease Surveillance T. Trends in Prevalence of Chronic Kidney Disease in the United States. *Ann Intern Med.* 2016;165:473-481.
3. Van Pottelbergh G, Vaes B, Jadoul M, Mathei C, Wallemacq P and Degryse JM. The prevalence and detection of chronic kidney disease (CKD)-related metabolic complications as a function of estimated glomerular filtration rate in the oldest old. *Arch Gerontol Geriatr.* 2012;54:e419-25.
4. Bowling CB, Inker LA, Gutierrez OM, Allman RM, Warnock DG, McClellan W and Muntner P. Age-specific associations of reduced estimated glomerular filtration rate with concurrent chronic kidney disease complications. *Clin J Am Soc Nephrol.* 2011;6:2822-8.
5. Bowling CB and Muntner P. Epidemiology of chronic kidney disease among older adults: a focus on the oldest old. *Journals of Gerontology Series A, Biological Sciences and Medical Sciences.* 2012;67:1379-86.

6. Brown MA, Collett GK, Josland EA, Foote C, Li Q and Brennan FP. CKD in elderly patients managed without dialysis: survival, symptoms, and quality of life. *Clin J Am Soc Nephrol*. 2015;10:260-8.
7. Okparavero A, Foster MC, Tighiouart H, Gudnason V, Indridason O, Gudmundsdottir H, Eiriksdottir G, Gudmundsson EF, Inker LA and Levey AS. Prevalence and complications of chronic kidney disease in a representative elderly population in Iceland. *Nephrol Dial Transplant*. 2016;31:439-47.
8. Clinical Practice Guidelines: KDIGO Guideline for CKD Classification and Management. 2012.
9. Arora P, Jalal K, Gupta A, Carter RL and Lohr JW. Progression of kidney disease in elderly stage 3 and 4 chronic kidney disease patients. *Int Urol Nephrol*. 2017;49:1033-1040.
10. Lundstrom UH, Gasparini A, Bellocco R, Qureshi AR, Carrero JJ and Evans M. Low renal replacement therapy incidence among slowly progressing elderly chronic kidney disease patients referred to nephrology care: an observational study. *BMC Nephrol*. 2017;18:59.
11. Xiong Z, Xu H, Huang X, Arnlov J, Qureshi AR, Cederholm T, Sjogren P, Lindholm B, Riserus U and Carrero JJ. Nonesterified fatty acids and cardiovascular mortality in elderly men with CKD. *Clin J Am Soc Nephrol*. 2015;10:584-91.
12. Liu IT, Wu JS, Yang YC, Huang YH, Lu FH and Chang CJ. Mild chronic kidney disease associated with greater risk of arterial stiffness in elderly adults. *Journal of the American Geriatrics Society*. 2013;61:1758-62.
13. Peralta CA, Lee A, Odden MC, Lopez L, Zeki Al Hazzouri A, Neuhaus J and Haan MN. Association between chronic kidney disease detected using creatinine and cystatin C and death and cardiovascular events in elderly Mexican Americans: the Sacramento Area Latino Study on Aging. *Journal of the American Geriatrics Society*. 2013;61:90-5.
14. Nitsch D, Nonyane BA, Smeeth L, Bulpitt CJ, Roderick PJ and Fletcher A. CKD and hospitalization in the elderly: a community-based cohort study in the United Kingdom. *Am J Kidney Dis*. 2011;57:664-72.
15. Michels WM, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW and Krediet RT. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. *Clin J Am Soc Nephrol*. 2010;5:1003-9.
16. Levey AS, Becker C and Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. *JAMA*. 2015;313:837-46.
17. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney International Supplements*. 2013;3:1-150.
18. Baxmann AC, Ahmed MS, Marques NC, Menon VB, Pereira AB, Kirsztajn GM and Heilberg IP. Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C. *Clin J Am Soc Nephrol*. 2008;3:348-54.
19. Shlipak MG, Matsushita K, Arnlov J, Inker LA, Katz R, Polkinghorne KR, Rothenbacher D, Sarnak MJ, Astor BC, Coresh J, Levey AS and Gansevoort RT. Cystatin C versus creatinine in determining risk based on kidney function. *The New England journal of medicine*. 2013;369:932-43.
20. Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, Siscovick DS and Stehman-Breen C. Cystatin C and the risk of death and cardiovascular events among elderly persons. *The New England journal of medicine*. 2005;352:2049-60.

21. Ballew SH, Chen Y, Daya NR, Godino JG, Windham BG, McAdams-DeMarco M, Coresh J, Selvin E and Grams ME. Frailty, Kidney Function, and Polypharmacy: The Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis.* 2017;69:228-236.
22. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA and Cardiovascular Health Study Collaborative Research G. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* 2001;56:M146-56.
23. Bandeen-Roche K, Seplaki CL, Huang J, Buta B, Kalyani RR, Varadhan R, Xue QL, Walston JD and Kasper JD. Frailty in Older Adults: A Nationally Representative Profile in the United States. *J Gerontol A Biol Sci Med Sci.* 2015;70:1427-34.
24. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T and Coresh J. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150:604-12.
25. Kucharska-Newton AM, Palta P, Burgard S, Griswold ME, Lund JL, Capistrant BD, Kritchevsky SB, Bandeen-Roche K and Windham BG. Operationalizing Frailty in the Atherosclerosis Risk in Communities Study Cohort. *J Gerontol A Biol Sci Med Sci.* 2017;72:382-388.
26. Schneider AL, Kalyani RR, Golden S, Stearns SC, Wruck L, Yeh HC, Coresh J and Selvin E. Diabetes and Prediabetes and Risk of Hospitalization: The Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care.* 2016;39:772-9.