1.a. Full Title: Obesity, Weight Distribution and Risk of Acute Kidney Injury in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Obesity and Risk of AKI

2. Writing Group:
   Writing group members: Keiko Greenberg, MD, Josef Coresh, MD, PhD, Lisa Wruck, PhD, Morgan Grams MD, PhD, others welcome

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

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3. Timeline:
   Data analysis will start immediately. A manuscript is expected to be prepared within 6 months.

4. Rationale:

   Acute kidney injury (AKI) is a frequent complication in hospitalized patients that is associated with significant morbidity and mortality (Xue et al 2006, Ali et al 2007, Lamiere et al 2013). Unfortunately, there are no specific treatments available for AKI.
Prevention of AKI, however, may be possible with the use of certain strategies, such as appropriate volume resuscitation and avoidance of iodinated contrast. Although there are several known risk factors for AKI, the identification of additional risk factors is important for identifying individuals who could benefit from strategies to prevent AKI.

Obesity has been associated with AKI in surgical and critically ill patients in several studies (Druml et al 2010, Billings et al 2012, Shashaty et al 2012, Bagshaw et al 2013, Kelz et al 2013). Potential mechanisms by which obesity could increase risk of AKI include oxidative stress, inflammation and intra-abdominal hypertension (Billings et al 2012, Wang et al 2004, Hung et al 2005, Holodinsky et al 2013, Suneja 2014). In studies to date, body mass index (BMI) has been used as the measure of obesity and measured just prior to or at the time of hospital admission. It is not known whether BMI measured months or years ahead of surgery or critical illness is also associated with AKI. In addition, it is not known whether other measures of adiposity, such as waist-to-hip ratio, are associated with risk of AKI. Data showing intra-abdominal pressure to be correlated to sagittal abdominal diameter (Sugerman et al 1997, Lambert et al 2005) suggest that measures of central obesity could be a risk factor for AKI independent of BMI.

We propose to assess whether BMI and waist-to-hip ratio measured well in advance of possible hospitalization are risk factors for hospitalized AKI independent of known risk factors for AKI in a general population.

5. Main Hypothesis/Study Questions:

1. Baseline BMI will be associated with hospitalized AKI independent of known AKI risk factors.

2. Baseline waist-to-hip ratio will be associated with hospitalized AKI independent of known AKI risk factors.

3. Baseline BMI and waist-to-hip ratio will be associated with hospitalized AKI independent of each other.

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.

Inclusion/exclusion: ARIC participants at visit 4. Visit 4 was used as the baseline because albuminuria was measured for the first time at that visit. Participants with history of hospitalized AKI, eGFR < 15ml/min/1.73m², and those who were missing BMI, waist-to-hip ratio or one or more covariates were excluded.
**Outcome:** Hospitalized AKI occurring between visit 4 and December 31, 2010. AKI was defined as the presence of the following diagnosis codes on discharge summaries and death certificates: ICD-9-CM codes 584.x and ICD-10-CM codes N17.x.

**Covariates:** Age, sex, race, eGFR, albuminuria, history of diabetes, history of hypertension, and prevalent coronary heart disease (all previously identified risk factors for AKI) at baseline (visit 4).

**Data analysis:** Baseline characteristics of the participants will be compared by BMI (< 30kg/m² vs ≥ 30kg/m²) and waist-to-hip ratio (for men: < 1.0 vs ≥ 1.0; for women: < 0.8 vs ≥ 0.8). The association between baseline BMI and baseline waist-to-hip ratio and risk of AKI will be modeled using Cox proportional hazards regression. Analyses will be adjusted for the above covariates; of note, eGFR will be modeled as a linear spline with knot at 60ml/min/m², and albuminuria will be log transformed. We will also adjust for time-varying hospitalizations to account for the possibility that obesity is associated with more frequent hospitalizations. In order to determine whether any identified association between measures of obesity and hospitalized AKI are driven by an increased number of interventions for coronary heart disease in obese participants, we will identify cardiac procedures using ICD codes and analyze hospitalized AKI with cardiac procedures and hospitalized AKI without cardiac procedures separately.

**Limitations:**
1. Use of diagnosis codes to define AKI has been shown to be very specific, but insensitive compared to KDIGO criteria (Grams 2014). To validate the associations between BMI, waist-to-hip ratio and hospitalized AKI observed in our analysis, we will examine a subset of participants hospitalized in Washington County for whom creatinine data is available during the study period. For this subset, hospitalized AKI will be defined using KDIGO criteria. Cox regression will be used to model the association between BMI and waist-to-hip ratio and creatinine-based AKI and the results compared to those for diagnosis code-defined AKI.

2. In many participants, hospitalized AKI will not occur until several years after baseline. This raises the possibility that any observed association between obesity and risk of hospitalized AKI is due to more rapid decline of renal function in obese participants compared to non-obese participants. To address this problem, we will analyze data for Washington County participants using eGFR as a time-varying variable.

3. We will also explore other analyses to address other limitations, such as including data on NSAID use at baseline as a covariate.

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.csccl.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)?

    #1944 Risk factors for acute kidney injury. M. Grams

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
      ___X__  A. primarily the result of an ancillary study (list number* _2011.03_)
       ____  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.csccl.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
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