ARIC Manuscript Proposal #2325

PC Reviewed: 3/11/14 **Status: A** **Priority: 2**
SC Reviewed: _________ **Status: _____** **Priority: ____**

1.a. Full Title: Relationship of dietary features related to acid load and subsequent kidney disease: Atherosclerosis Risk in Communities study

b. Abbreviated Title (Length 26 characters): Acid Load and Kidney Disease

2. Writing Group:
Writing group members: Casey M. Rebholz, Morgan E. Grams, Lyn M. Steffen, Deidra C. Crews, Lawrence J. Appel, Josef Coresh, others welcome

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

First author: Casey M. Rebholz
Address: Johns Hopkins Bloomberg School of Public Health
Welch Center for Prevention, Epidemiology and Clinical Research
2024 E. Monument Street, Suite 2-600
Baltimore, MD 21287
Phone: 410-502-2049 Fax: 410-955-0476
E-mail: crebholz@jhsph.edu

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).

Name: Josef Coresh
Address: Johns Hopkins Bloomberg School of Public Health
Welch Center for Prevention, Epidemiology and Clinical Research
2024 E. Monument Street, Suite 2-600
Baltimore, MD 21287
Phone: 410-955-0495 Fax: 410-955-0476
E-mail: coresh@jhu.edu

3. Timeline: Upon manuscript proposal approval, data analysis will begin. The authors anticipate that the analysis and writing process will take one year.

4. Rationale:

Recommended nutritional management of chronic kidney disease includes dietary protein restriction and avoidance of high protein intake (1). The Modification of Diet in Kidney Disease randomized clinical trials demonstrated no sustained, significant decline in renal disease progression with dietary protein restriction (2). However, two subsequent meta-analyses of randomized controlled trials reported that dietary protein restriction slows the rate of decline in kidney function (3, 4).

Furthermore, there is evidence suggesting that increased dietary protein intake may promote kidney damage among individuals with reduced kidney function through increased glomerular pressure and hyper-filtration (5, 6). In the OmniHeart trial, among individuals with normal kidney function [mean estimated glomerular filtration rate (eGFR) 92 mL/min/1.73 m^2], a higher protein diet increased cystatin C-based eGFR by about 4 mL/min/1.73 m^2 over six weeks, which was thought to be a maladaptive response (7). Otherwise, there is limited evidence on the relationship between protein intake and kidney damage for individuals with normal kidney function.

The mixed findings in the literature may be due to a dietary characteristic other than protein that is responsible for slowing the rate of kidney function decline, such as dietary acid load (8). For example, in the African American Study of Kidney Disease and Hypertension (AASK) cohort study, higher quartiles of estimated net endogenous acid production were significantly associated with faster decline in estimated glomerular filtration rate (p for trend=0.01 in adjusted analyses) (9). Other dietary features that impact acid load which may be associated with kidney disease include source of protein (animal vs. vegetable), consumption of fruits and vegetables, and dietary phosphate intake (10-12).

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

The overall objective of the proposed study is to assess the relationship between dietary characteristics related to acid load and subsequent kidney disease outcomes among ARIC study participants by testing the following hypotheses:

1) Higher levels of daily protein intake (% of total calories from protein/day, grams of protein/day) are associated with higher risk of kidney disease.
    a. Less consumption of protein from vegetable sources than animal sources (% of total calories from vegetable protein/day, proportion of total daily protein from vegetable sources) is associated with higher risk of kidney disease.

2) Fewer servings of fruits and vegetables is associated with higher risk of kidney disease.

3) Higher dietary acid load is associated with higher risk of kidney disease.

4) Higher dietary phosphate intake (% of total calories from phosphate/day, absolute milligrams of daily phosphate intake) is associated with higher risk of kidney disease.

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 analysis of the ARIC cohort from baseline (study visit 1, 1986-1989) through follow-up (December 31, 2010)

Eligibility: ARIC study participants with missing dietary data will be excluded.

Dietary Assessment:

Dietary characteristics (daily protein intake overall and by protein source estimated as percent of total calories and grams, number of daily servings of fruits and vegetables, daily phosphate intake estimated as percent of total calories and grams) will be estimated from the semi-quantitative, 66-item food frequency questionnaire, modified from the Willett questionnaire (13). The reliability of this questionnaire was assessed within ARIC (14). The questionnaire was administered by trained interviewers at the baseline examination (1986-1989). Participants reported how often they consumed each food item of a specified portion size on average during the last year in the following categories: almost never, 1-3/month, 1/week, 2-4/week, 5-6/week, 1/day, 2-3/day, 4-6/day, >6/day. Individual food items were classified into food groups (e.g. fruits, vegetables). The daily intake of various nutrients (e.g. protein, phosphate, calories) was calculated at the Channing Laboratory, Harvard Medical School, by multiplying each food item by their nutrient content. Nutrient content for each food item was estimated from U.S. Department of Agriculture sources (15, 16). Dietary acid load will be estimated using the net endogenous acid production, as the ratio of protein to potassium intake (8).

Outcome Ascertainment:

The primary endpoint will be *end-stage renal disease*, identified through the U.S. Renal Data System (USRDS) registry, through December 31, 2010. Several additional kidney outcome variables will be assessed. *Kidney failure* will be defined as kidney failure-related hospitalizations and deaths identified through ARIC cohort surveillance, through December 31, 2010. *Chronic kidney disease* will be defined as eGFR <60 mL/min/1.73 m^2 at a subsequent study visit and eGFR decline of at least 25% from baseline, USRDS-identified end-stage renal disease, or chronic kidney disease-related hospitalization or death. *Prevalent albuminuria* will be defined moderately increased albuminuria (A2: 30-300 mg/g) or severely increased albuminuria (A3: >300 mg/g) at a subsequent study visit (1).

Statistical Analysis:

We will calculate time from study enrollment until kidney disease outcome, or censoring due to death or loss to follow-up. We will incorporate this time variable into survival analysis methods to assess the association between diet characteristics (protein source, fruits and vegetables, acid load, phosphate) and kidney disease.

Important covariates to include in multivariable regression models include measurements of baseline kidney function [estimated glomerular filtration rate (eGFR)], demographics (age, sex, race), anthropometrics (body mass index, waist circumference, weight), other clinical measures (blood pressure, high-density lipoprotein cholesterol), medical history (diabetes status, history of cardiovascular disease), and health behavior characteristics (smoking status, physical activity). In addition, we will need to consider the potential effect of other diet characteristics on the risk of kidney disease in this study population, namely calories, fat, sodium, potassium, and phosphate, by multivariable adjustment and expressing the exposure of interest as a proportion of total caloric intake. Analyses will be repeated after stratifying by baseline kidney function (eGFR < 60, 60-89, or ≥ 90 mL/min/1.73 m^2).

Potential Limitations/Challenges:

There may be measurement error in the assessment of dietary intake using self-report and a single questionnaire. We will express dietary consumption relative to total caloric intake, in addition to absolute intake. We will expand upon the published reliability study to include measures of interest in the present proposed study (14).

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? __X__ 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"?
__X__ 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)?

#224: Dietary risk factors for decreased renal function in the ARIC study (lead author: Josef Coresh)

#348: Dietary risk factors for 9-year incidence of decreased renal function in the ARIC study (lead author: Josef Coresh)

#1209: Food, dietary patterns, and prevalence of microalbuminuria in the Atherosclerosis, Plaque and CVD in Communities Study (lead author: Jennifer Nettleton)

To the best of our knowledge, none of the above listed proposals resulted in publications. As such, we do not anticipate that overlap of study questions will be an issue. Furthermore, Dr. Josef Coresh, the lead author or member of the writing group of all three proposals listed above is involved in and supportive of the current proposal.

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.

References

1. (KDIGO) KDIGO. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International Supplements. 2013;3(1):1-150.

2. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. The New England journal of medicine. 1994;330(13):877-84.

3. Kasiske BL, Lakatua JD, Ma JZ, Louis TA. A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. American journal of kidney diseases : the official journal of the National Kidney Foundation. 1998;31(6):954-61.

4. Pedrini MT, Levey AS, Lau J, Chalmers TC, Wang PH. The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. Annals of internal medicine. 1996;124(7):627-32.

5. Dunkler D, Dehghan M, Teo KK, Heinze G, Gao P, Kohl M, et al. Diet and kidney disease in high-risk individuals with type 2 diabetes mellitus. JAMA internal medicine. 2013;173(18):1682-92.

6. Martin WF, Armstrong LE, Rodriguez NR. Dietary protein intake and renal function. Nutrition & metabolism. 2005;2:25.

7. Juraschek SP, Appel LJ, Anderson CA, Miller ER, 3rd. Effect of a high-protein diet on kidney function in healthy adults: results from the OmniHeart trial. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2013;61(4):547-54.

8. Scialla JJ, Anderson CA. Dietary acid load: a novel nutritional target in chronic kidney disease? Advances in chronic kidney disease. 2013;20(2):141-9.

9. Scialla JJ, Appel LJ, Astor BC, Miller ER, 3rd, Beddhu S, Woodward M, et al. Net endogenous acid production is associated with a faster decline in GFR in African Americans. Kidney international. 2012;82(1):106-12.

10. Bernstein AM, Treyzon L, Li Z. Are high-protein, vegetable-based diets safe for kidney function? A review of the literature. Journal of the American Dietetic Association. 2007;107(4):644-50.

11. Goraya N, Simoni J, Jo C, Wesson DE. Dietary acid reduction with fruits and vegetables or bicarbonate attenuates kidney injury in patients with a moderately reduced glomerular filtration rate due to hypertensive nephropathy. Kidney international. 2012;81(1):86-93.

12. Gutierrez OM, Wolf M. Dietary phosphorus restriction in advanced chronic kidney disease: merits, challenges, and emerging strategies. Seminars in dialysis. 2010;23(4):401-6.

13. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. American journal of epidemiology. 1985;122(1):51-65.

14. Stevens J, Metcalf PA, Dennis BH, Tell GS, Shimakawa T, Folsom AR. Reliability of a food frequency questionnaire by ethnicity, gender, age and education. Nutr Res. 1996;16(5):735-45.

15. Composition of Foods: Agriculture Handbook No. 8 series. Washington, DC: Human Nutrition Information Service, US Department of Agriculture, 1975-1989.

16. Matthews RH, Pehrsson PR, Farhat-Sabet M. Sugar content of selected foods: individual and total sugars. Washington, DC: U.S. Department of Agriculture, 1987.