ARIC Manuscript Proposal #2674

PC Reviewed: 12/8/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Association of dietary protein sources with incident chronic kidney disease (CKD) and end-stage renal disease (ESRD). Results from the Atherosclerosis Risk in the Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):
Dietary protein sources and kidney disease

2. Writing Group:

Dr. Bernhard Haring	email: Haring_B@ukw.de
Dr. Josef Coresh	email: coresh@jhu.edu
Dr. Elizabeth Selvin	email: eselvin@jhu.edu
Dr. Morgan Grams	email: mgrams2@jhmi.edu
Dr. Casey Rebholz	email: crebhol1@jhu.edu

I, *Bernhard Haring* (the first author), confirm that all the coauthors have given their approval for this manuscript proposal.

First author: Bernhard Haring, MD MPH
Department of Internal Medicine I
University of Würzburg
Würzburg, Bavaria, Germany
Email: Haring_B@ukw.de
Phone: +49 176 5959 1627
Fax: +49 931 201 639001

3. July 2010 NHLBI workshop at Northwestern University
The first author has participated in the July2010 NHLBI workshop at Northwestern University.

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: Casey Rebholz, PhD
Welch Center for Prevention, Epidemiology and Clinical Research
Johns Hopkins Univeristy
Baltimore, Maryland 21287
Email: crebhol1@jhu.edu

4. Timeline / Analyses
Data preparation and analysis will begin upon approval, and manuscript drafting will commence once suitable analytical models are finalized. The expected timeline is 2016-2017.

5. Rationale

Dietary protein intake can modulate renal function and its role in renal disease has been debated for decades.[1-3] Conclusions such as "too much protein stresses the kidney" have been recited from physiology textbooks to media coverage. At the center is the concern that consumption of dietary protein in excess of recommended amounts promotes renal disease through increased glomerular pressure and hyperfiltration. Indeed, controlled feeding studies in humans indicate that an increase in the glomerular filtration rate can be induced by animal protein.[2, 4-6] In contrast, consumption of vegetable protein and egg whites produces little or no effect.[4, 5] The pathophysiological explanation for this is not fully understood but may involve lower concentrations of amino acids that cause renal vasodilation and lesser stimulation of vasodilator prostaglandins.[5] On the other hand, dietary protein sources vary in their non-protein constituents (e.g. sodium content), which may in part explain differential health effects. Food group analyses of major dietary protein sources instead of nutrient analysis (‘dietary protein type’) are thus warranted. In fact, there is growing evidence showing the adverse health effects of red and processed meat intake in contrast to animal protein intake per se.[7-10] However, to this point evidence derived from comprehensive food group analyses with regards to incident kidney disease in otherwise healthy persons is missing.

6. Research Hypothesis

The primary objective of this study is to evaluate the relationship between individual protein-rich food groups on the risk of incident chronic kidney disease (CKD) and end-stage renal disease (ESRD) in a large, community-based cohort of middle-aged adults.

We hypothesize that animal derived food groups such as red or processed meat will be associated with an increased risk for incident CKD and ESRD. We hypothesize that plant-based proteins such as nuts and legumes will be associated with a reduced risk of incident CKD and ESRD.

7. Design and analysis

Study Population

The Atherosclerosis Risk in Communities Study (ARIC) is a community-based prospective cohort study of 15,792 middle-aged adults (aged 45-64 years at baseline) from four U.S. communities.[11] For this analysis, only white and black adults will be included; blacks from the Minneapolis and Washington County field centers will be excluded due to small numbers. Individuals with self-reported diabetes, fasting blood glucose ≥ 126 mg/dL, non-fasting blood glucose ≥ 200 mg/dL or use of diabetes medication, a history of renal failure, a history of myocardial infarction, stroke, heart failure, coronary bypass surgery, angioplasty or with missing data on covariates of interest will not be included in our analyses as these conditions may lead to changes in diet and therefore the FFQ may not be a good representation of usual long-term diet. Participants with incomplete dietary information or with extreme calorie intake (<600 kcal or > 4200 kcal per day for men, <500 kcal or > 3600 kcal per day for women) will also be excluded from further analysis. Last, for the purposes of the present study, only participants free of CKD [i.e. estimated glomerular filtration (eGFR) ≥60 mL/min/1.73 m^2] will be included.

Assessment of protein intake

The ARIC study assessed protein intake using an interviewer-administered, 66-item food frequency questionnaire (FFQ) adapted from the 61-item FFQ developed by Willett et al.[12] The FFQ was administered to all subjects at visit 1 at baseline (1987–1989) and at visit 3

(1993–1995). The major contributors to protein intake included: unprocessed red meat, processed red meat, poultry, high-fat dairy, low-fat dairy, fish & seafood, eggs, nuts, and legumes. Vegetable protein intake will be defined as the difference of total and animal protein intake.
For assessing dietary behaviour, participants will be divided into quintiles of cumulative average intake of various protein sources. Cumulative updating of the FFQ (i.e. visit 1 FFQ for follow-up between visit 1 and visit 3 and the average of visits 1 and 3 FFQ afterwards for those who attended both examinations, or visit 1 FFQ for those who did not attend visit 3) will be used to reduce within-person variation and best represent long-term dietary behavior [9].

Assessment of kidney disease
The primary endpoints for this study will be incident CKD stage 3 and incident ESRD after 1987. In the ARIC study, creatinine values were converted to eGFR using the 2009 CKD-Epi creatinine equation. Incident CKD stage 3 will be defined as a decrease in eGFR of at least 25% from baseline resulting in a final eGFR of less than 60 mL/min/1.73 m^2, CKD-related hospitalizations or deaths, or incident ESRD. Incident ESRD will be identified through the US Renal Data System (USRDS) registry, through December 31, 2010.[13-15]
Secondary endpoints for this study will be incident prevalent albuminuria and kidney failure: Prevalent albuminuria will be defined as presence of microalbuminuria (i.e. 30-300mg/g) or macroalbuminuria (>300mg/g). Kidney failure will be defined as kidney failure-related hospitalizations and deaths identified through ARIC cohort surveillance.[15]

Covariates
Height, weight, and waist circumference were measured following a standardized protocol. [11, 16] ARIC participants underwent fasting venipuncture at each examination.[11] Data on current smoking, ethanol intake, education, intake of antihypertensive or lipid lowering medication were derived from standardized questionnaires.[11] Sports-related physical activity and leisure related physical activity were assessed with the use of Baecke's questionnaire and scoring systems.[17] Hypertension will be defined as the average of the last two of three blood-pressure readings at the first visit (using 140mmHg or higher for systolic and 90mmHg or higher for diastolic as cut-off points). Diabetes status will be coded positive in individuals with self-reported diabetes, fasting blood glucose $\geq$ 126 mg/dL, non-fasting blood glucose $\geq$ 200 mg/dL or use of diabetes medication.

Statistical Analysis
Mean values for continuous variables and proportions for categorical variables will be used to describe baseline characteristics (ARIC visit 1, 1987-1989) of the study participants.
To assess the association of dietary protein sources (food groups) with CKD (Table 2) or ESRD incidence (Table 3) , we will calculate incidence rates (IR) of outcome events per 1000 person-years as the number of diagnosed cases of CKD or ESRD cases occurring during the entire follow-up period divided by person-years of follow-up. Person-years of follow up will be defined as time from the baseline examination to the date of the first outcome event, death, lost to follow-up, or December 31, 2010. Thereafter, corresponding rate ratios will be calculated by dividing the rate among participants in each specific intake quintile by the rate among participants in the lowest quintile of intake (reference). Cox proportional hazards regression models will be used to account for potential confounding. An initial model will adjust for age, race, sex, ARIC study center, and total energy intake (minimally adjusted model). A second model will additionally adjust for smoking (current, former, never), pack years of smoking, education (less than high school, high school, more than high school),

systolic blood pressure (mmHg), use of antihypertensive medication, HDLc (mmol/l), diabetes status, total cholesterol (mmol/l), use of lipid lowering medication, body mass index (kg/m^2), waist-to-hip ratio, alcohol intake (g/week), Baecke's physical activity score, leisure-related physical activity and carbohydrate intake (quintiles) (fully adjusted model).
Finally, we will assess the relationship between dietary protein sources and incident albuminuria (micro-/macroalbuminuria) or kidney failure (Table 4a/b & 5) as described above.

8. Conclusion
We anticipate that certain animal sources of protein such as red meat and processed meat products will be associated with an increased risk for CKD and ESRD and that vegetable sources of protein such as nuts and legumes will be associated with a reduced risk of CKD and ESRD.

9.a. Will the data be used for non-CVD analysis in this manuscript? No

9.b. NA

10.a. Will the DNA data be used in this manuscript? No

10.b. NA

11.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. Yes

12. 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)?

ARIC manuscript proposal #2325: 'Relationsship of dietary features related to acid load and subsequent kidney disease'

13. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? No

14a. 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.
Yes, the lead author is aware that manuscript preparation is expected to be completed in 1-3 years, and if this expectation is not met, the manuscript proposal will expire.

14.b. 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. Yes, the lead author is aware of the Public Access Policy and that manuscript has to be uploaded to PubMed Central.

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Table 1. Unadjusted baseline characteristics according to kidney failure status, ARIC 1987-1989

	No CKD or ESRD	**CKD**	**ESRD**
N			
Age, years (SD)			
Women, %			
Black, %			
High school graduate, %			
Current smoker, %			
Body Mass Index, kg/m^2 (SD)			
Waist-to-hip ratio (SD)			
Baecke Sport Activity Score (SD)			
Baecke Leisure Index (SD)			
Hypertension, %			
Systolic blood pressure, mmHg (SD)			
Use of antihypertensive medication, %			
Diabetes, %			
Serum cholesterol, mmol/L (SD)			
Serum HDL, mmol/L (SD)			
Use of lipid lowering medication, %			
Alcohol intake, g/week (SD)			
Total energy intake, kcal/day (SD)			
Protein intake, g/day (SD)			
Protein intake, % of total energy			
Carbohydrate intake, g/day (SD)			
Carbohydrate intake, % of total energy (SD)			
Total fat Intake (g/d) (Median ±SD)			
Total fat intake, % of total energy (SD)			

eGFR (ml/min/1.73m2)			
Albuminuria			
<30mg/g			
30-300mg/g			
>300mg/g			

Values are % for categorical variables and mean (SD) for continuous variables.

Table 2/3. Association of major dietary protein sources with incident CKD / with incident ESRD, ARIC 1987 – 2010

	Q 1	Q 2	Q 3	Q 4	Q 5	p-trend
Processed Meat						
Median svg/day						
HR (95%CI)*	1 (ref)					
HR (95%CI)**	1 (ref)					
Red Meat						
Median svg/day						
HR (95%CI)*	1 (ref)					
HR (95%CI)**	1 (ref)					
Red Meat & Processed Meat						
Median svg/day						
HR (95%CI)*	1 (ref)					
HR (95%CI)**	1 (ref)					
Poultry						
Median svg/day						
HR (95%CI)*	1 (ref)					
HR (95%CI)**	1 (ref)					
Dairy						
Median svg/day						
HR (95%CI)*	1 (ref)					
HR (95%CI)**	1 (ref)					
High-Fat Dairy						

Median svg/day						
HR (95%CI)*	1 (ref)					
HR (95%CI)**	1 (ref)					
Low-Fat Dairy						
Median svg/day						
HR (95%CI)*	1 (ref)					
HR (95%CI)**	1 (ref)					
Fish & seafood						
Median svg/day						
HR (95%CI)*	1 (ref)					
HR (95%CI)**	1 (ref)					
Eggs						
Median svg/day						
HR (95%CI)*	1 (ref)					
HR (95%CI)**	1 (ref)					
Nuts						
Median svg/day						
HR (95%CI)*	1 (ref)					
HR (95%CI)**	1 (ref)					
Legumes						
Median svg/day						
HR (95%CI)*	1 (ref)					
HR (95%CI)**	1 (ref)					

*adjusted for age, sex, race, study, center, and total energy intake

** adjusted for age, sex, race, study center, total energy intake, smoking, education, systolic blood pressure, use of antihypertensive medication, HDLc, total cholesterol, use of lipid lowering medication, diabetes status, body mass index, waist-to-hip ratio, alcohol intake, sports-related physical activity, leisure-related physical activity and carbohydrate intake.

Table 4a/b & 5. Association of major dietary protein sources with incident proteinuria (micro- or macroalbuminuria) & with incident kidney failure status, ARIC 1987 – 2010