ARIC Manuscript Proposal # 3155

1.a. Full Title: Diet quality scores and incident kidney disease in the ARIC study.

b. Abbreviated Title (Length 26 characters): Diet scores and CKD

2. Writing Group:
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   Others welcome

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

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3. Timeline: This manuscript proposal is one of three aims in Emily Hu’s PhD dissertation. We plan to start analysis upon manuscript approval and complete the paper within two years.
4. **Rationale:**
Chronic kidney disease (CKD) affects between 11-13% of adults in the world and poses a major global public health problem [1]. In order to reduce the risk of CKD, clinical measures such as preventing and controlling diabetes and hypertension are implemented [2]. However, evidence suggests that lifestyle modifications such as increasing physical activity, reducing weight, and modifying diet also play a vital role in reducing the risk of kidney disease [3].

Diet is an essential component of one’s lifestyle that can be modified to prevent and reduce the onset of chronic conditions such as type 2 diabetes and cardiovascular disease. Healthy dietary patterns such as the Dietary Approaches to Stop Hypertension (DASH) diet and Mediterranean diet have been shown to reduce the risk of hypertension, cardiovascular disease, and related chronic diseases [4-7]. Diet scores used to measure adherence to the U.S. Dietary Guidelines for Americans such as the Healthy Eating Index (HEI) and the Alternative Healthy Eating Index (AHEI) have also been shown to be associated with reduced risk of chronic diseases [8, 9]. The Mediterranean diet has been shown to reduce the incidence of major cardiovascular events among people with high cardiovascular risk in the PREDIMED study [10]. A similar index known as the alternate Mediterranean diet score (aMed) has been developed based on the Mediterranean diet to be applied to US populations [11]. Because CKD shares many risk factors with diabetes and cardiovascular disease, adherence to these dietary patterns may also reduce the risk of incident CKD.

Although the Mediterranean diet, HEI, and AHEI scores are associated with reduced adverse health outcomes in the general population, there is not sufficient evidence that these scores can be applicable to patients who are at risk of kidney disease. There are no current dietary guidelines for the prevention of kidney disease; however, clinicians typically recommend kidney disease patients to focus on the reduction of isolated nutrients such as protein, sodium, potassium, and phosphorus. It would be of interest to examine the relationship between overall dietary patterns and risk of incident kidney disease. To date, several studies, including the ARIC study, have examined the association between the DASH diet and incident CKD and found that higher adherence to the DASH diet is associated with lower risk of CKD [12-15]. However, few studies have examined the association between diet patterns and kidney disease using the Mediterranean diet score or HEI and AHEI indices. A study in the National Institutes of Health – American Association of Retired Persons (NIH-AARP) cohort found that diet quality assessed by the AHEI-2010, HEI-2010, Mediterranean Diet Score, and DASH score were inversely associated with a composite outcome of death due to a renal cause and dialysis [16]. However, this study was primarily made up of Caucasians and they did not have measures of eGFR or proteinuria. Researchers also found that higher scores (indicating greater adherence) for the Mediterranean diet and lower risk of reduced kidney function (eGFR<60 mL/min/1.73 m²) in the Northern Manhattan Study [17]. However, this study was small (N=900) and the primary outcome was solely based on eGFR.

Given the lack of studies in this area, we seek to investigate the associations between the Mediterranean diet, HEI-2015, and AHEI-2010 scores and incident kidney disease in the ARIC study.

5. **Main Hypothesis/Study Questions:** We hypothesize that higher scores indicating greater adherence for the alternative Mediterranean (aMed) diet score, HEI-2015, and AHEI-2010 are associated with a lower risk of incident kidney disease in participants from the ARIC study.
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 study, including participants from baseline (Visit 1, 1987-1989) through Dec 31, 2013. We will exclude participants who are missing food frequency questionnaire (FFQ) data, have kidney disease at baseline (eGFR<60 mL/min/1.73 m²), or who have implausible values for total caloric intake (<500 or >3,500 kcal/d for women; <700 or >4,500 kcal/d for men). We will also exclude participants with missing covariates.

Exposure:
The 3 primary exposures are the alternate Mediterranean diet score, the HEI-2015 score, and the AHEI-2010 score. Diet scores will be coded using the FFQ responses at visits 1 and 3.

Alternate Mediterranean diet score (aMed) [11]:
- Ranges from 0 (lowest) to 9 (highest)
- 9 components (vegetables excluding potatoes, fruits, nuts, whole grains, legumes, fish, fatty acids, red and processed meats, alcohol)
- Each of the first 7 components will be scored 1 if they are above the median intake; otherwise 0; red and processed meats will be scored 1 if they are below the median intake; otherwise 0; alcohol will be scored 0 or 1 based on sex-specific cutoffs

HEI-2015 score:
- Ranges from 0 to 100
- 13 components (total fruits, whole fruits, total vegetables, greens and beans, whole grains, dairy, total protein, seafood and plant protein, fatty acids, refined grains, sodium, added sugars, and saturated fats)
- Each component is scored based on whether the participant meets the cutoff

AHEI-2010 score [8]:
- Ranges from 0 to 110
- 11 components (fruits, vegetables, sugar-sweetened beverages and juices, nuts and legumes, whole grains, alcohol, omega-3 fatty acids, trans fats, polyunsaturated fatty acids, sodium, and red meat)
- Similar to the HEI-2015 index, each component receives a score based on cutoff
<table>
<thead>
<tr>
<th></th>
<th>HEI-2015 (100 points)</th>
<th>AHEI-2010 [8] (110 points)</th>
<th>aMed (9 points)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Min</td>
<td>Max</td>
<td>Min</td>
</tr>
<tr>
<td><strong>Total Vegetables</strong></td>
<td>0 points</td>
<td>5 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>0 cups/1000 kcal</td>
<td>≥1.1 cups/1000 kcal</td>
<td>0 servings</td>
</tr>
<tr>
<td><strong>Greens &amp; Beans</strong></td>
<td>0 points</td>
<td>5 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>0 cups/1000 kcal</td>
<td>≥0.2 cups/1000 kcal</td>
<td>0 servings</td>
</tr>
<tr>
<td><strong>Total Fruit</strong></td>
<td>0 points</td>
<td>5 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>0 cups/1000 kcal</td>
<td>≥0.8 cups/1000 kcal</td>
<td>0 servings</td>
</tr>
<tr>
<td><strong>Whole Fruit</strong></td>
<td>0 points</td>
<td>5 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>0 cups/1000 kcal</td>
<td>≥0.4 cups/1000 kcal</td>
<td>0 servings</td>
</tr>
<tr>
<td><strong>Whole grains</strong></td>
<td>0 points</td>
<td>10 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>0 oz/1000 kcal</td>
<td>≥1.5 oz/1000 kcal</td>
<td>0g/day</td>
</tr>
<tr>
<td><strong>Refined grains</strong></td>
<td>10 points</td>
<td>0 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>≥4.3oz/1000 kcal</td>
<td>≤1.8 oz/1000 kcal</td>
<td>0 servings</td>
</tr>
<tr>
<td><strong>All Dairy</strong></td>
<td>0 points</td>
<td>10 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>0 cups/1000 kcal</td>
<td>≥1.3 cups/1000 kcal</td>
<td>0 servings</td>
</tr>
<tr>
<td><strong>Sugar sweetened beverages</strong></td>
<td>0 points</td>
<td>5 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>≥1 servings</td>
<td>0 servings</td>
<td></td>
</tr>
<tr>
<td><strong>Total Protein</strong></td>
<td>0 points</td>
<td>5 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>0 oz/1000 kcal</td>
<td>≥2.5oz/1000 kcal</td>
<td></td>
</tr>
<tr>
<td><strong>Nuts &amp; Legumes</strong></td>
<td>0 points</td>
<td>10 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>0 servings</td>
<td>≥1 servings</td>
<td></td>
</tr>
<tr>
<td><strong>Red/processed meat</strong></td>
<td>0 points</td>
<td>10 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>≥1.5 servings</td>
<td>0 servings</td>
<td></td>
</tr>
<tr>
<td><strong>Seafood or Plant</strong></td>
<td>0 points</td>
<td>5 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>0 oz/1000 kcal</td>
<td>≥0.8 oz/1000 kcal</td>
<td></td>
</tr>
<tr>
<td><strong>Fish</strong></td>
<td>0 points</td>
<td>10 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>0 oz/1000 kcal</td>
<td>≥0.8 oz/1000 kcal</td>
<td></td>
</tr>
<tr>
<td><strong>Trans fat</strong></td>
<td>0 points</td>
<td>10 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>≥4% energy</td>
<td>≤0.5% energy</td>
<td></td>
</tr>
<tr>
<td><strong>Long-chain fats</strong></td>
<td>0 points</td>
<td>10 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>0 mg/day</td>
<td>250 mg/day</td>
<td></td>
</tr>
<tr>
<td><strong>PUFA</strong></td>
<td>0 points</td>
<td>10 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>≤2% energy</td>
<td>≥10% energy</td>
<td></td>
</tr>
<tr>
<td><strong>MUFA:SFA</strong></td>
<td>0 points</td>
<td>10 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>≤1.2</td>
<td>≥2.5</td>
<td></td>
</tr>
<tr>
<td><strong>(MUFA+PUFA)/SFA</strong></td>
<td>0 points</td>
<td>10 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>≤1.2</td>
<td>≥2.5</td>
<td></td>
</tr>
<tr>
<td><strong>Saturated fats</strong></td>
<td>0 points</td>
<td>10 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>≥16% energy</td>
<td>≤8% energy</td>
<td></td>
</tr>
<tr>
<td><strong>Sodium (mg/day)</strong></td>
<td>0 points</td>
<td>10 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>≥2.0g/1000 kcal</td>
<td>≤1.1g/1000 kcal</td>
<td>Highest decile</td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td>0 points</td>
<td>10 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>≥2.5 drinks</td>
<td>0.5-1.5 drinks</td>
<td></td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>0 points</td>
<td>10 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>≥2.5 drinks</td>
<td>0.5-1.5 drinks</td>
<td></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>0 points</td>
<td>10 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>≥3.5 drinks</td>
<td>0.5-2.0 drinks</td>
<td></td>
</tr>
<tr>
<td><strong>Added sugars</strong></td>
<td>0 points</td>
<td>10 points</td>
<td>0 points</td>
</tr>
<tr>
<td></td>
<td>≥26% energy</td>
<td>≤6.5% energy</td>
<td></td>
</tr>
</tbody>
</table>
Outcomes: Our primary 2 outcomes for all analyses are incident CKD and ESRD. For incident CKD, we will use the composite definition and visit-based measures as a sensitivity analysis. For ESRD, we will use USRDS data and the kidney failure definition as a sensitivity analysis. Furthermore, we will use cardiovascular disease and all-cause mortality as additional endpoints.

Primary Outcomes
A. Incident CKD (composite) defined by at least 1 of the following 4 criteria [18]:
   1) Development of reduced kidney function (eGFR <60 ml/min/1.73 m²) accompanied by at least 25% eGFR decline at any subsequent study visit relative to baseline
   2) International Classification of Diseases (IC)-9/10 code for a hospitalization related to CKD stage 3+ identified through active surveillance of the ARIC cohort
   3) ICD 9/10 code for a death related to CKD stage 3+ identified through linkage to the National Death Index
   4) End-stage renal disease identified by linkage to the US Renal Data System (USRDS) registry

B. Incident CKD using visit-based measures (sensitivity analysis for composite definition)
   1) eGFR <60 ml/min/1.73 m² and ≥30% eGFR decline

Secondary Outcomes
C. ESRD cases identified by US Renal Data System (USRDS)

D. Kidney failure – composite definition to use as a sensitivity analysis for ESRD cases [19]
   1) USRDS data to identify treated kidney failure
   2) ICD-9-CM and ICD-10-CM codes from hospitalizations and deaths that represented kidney failure, transplantation, and dialysis
   3) A study visit eGFR<15 mL/min/1.73 m² calculated with the Chronic Kidney Disease Epidemiology Collaboration creatinine equation [20]

E. Incident cardiovascular outcomes
   1) Incident CHD defined as definite or probable myocardial infarction or definite coronary death
   2) Stroke (ischemic or hemorrhagic) defined as sudden or rapid onset of neurological symptoms lasting for at least 24 hours or leading to death
   3) Incident heart failure: ICD-9 code 428 or ICD-10 code I50 in a hospitalization or death certificate

F. All-cause mortality – identification of death by telephone contact with participant proxy, obituaries, hospital records, death certificates, or vital statistics from the National Death Index

Covariates: We will use the following variables as covariates: sex, race-center, age, health behaviors (physical activity, smoking), socioeconomic status (education), family history of CVD, medical data (blood pressure, serum glucose, baseline eGFR), diabetes status, hypertension status (medication use and BP), BMI.
Main Analyses:
1) We will assess differences in demographic risk factors and other kidney disease risk factors according to quintiles of each diet index
2) We will estimate the hazard ratios and associated 95% CIs for incident risk of CKD and ESRD associated with quintiles of diet scores using Cox regression models (reference=quintile 1). Specifically, we aim to evaluate whether higher adherence to these diet indices are associated with lower risk for kidney disease. We will test for proportional hazards using Schoenfeld's residuals.
   a. Model 1: Total energy intake
   b. Model 2: Additionally adjusted for race, center, age, sex, baseline eGFR
   c. Model 3: Model 2+ adjusted for physical activity, smoking, family history of CVD, and education
   d. Model 4: Model 3+ adjusted for blood pressure, serum glucose, diabetes status, hypertension status, and BMI
   e. Model 5: Model 4+adjusted for SSBs (for aMed only), processed foods (chips, candy)
3) In addition to quintiles, we will use similar models as in #2 except with diet scores as a continuous variable assuming linearity and expressing the hazard ratio as per one point increase.
4) We will repeat the models in #2 using restricted cubic spline models to evaluate the shape of the association.
5) We will also use a cumulative average approach for the exposure by taking the average of foods from visits 1 and 3 and then creating diet scores. For participants who were censored between visits 1 and 3, we will create diet scores using visit 1 dietary data.
6) We will also estimate the hazard ratio for kidney disease within a subgroup of people with CVD at baseline, and by BMI categories, hypertension status, and diabetes status.
7) We will estimate competing risk of all-cause mortality prior to development of kidney disease using cumulative incidence function (stcrreg, stcurve command)
8) We will examine the association between individual components of each diet pattern and CKD.

Limitations:
A potential limitation of this study is that there was a gap in time with respect to in-person clinical examinations between 1998 and 2011. However, we have supplemented data with surveillance efforts to identify hospitalizations and deaths and we have linked to a registry to ascertain cases of end-stage renal disease. In addition, there may be measurement error in dietary assessment due to use of the self-reported food frequency questionnaires.

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.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)?

Manuscript proposals:
MS #1209: Foods, dietary patterns, and prevalence of microalbuminuria in the Atherosclerosis, Plaque, and CVD in Communities Study

MS #2325: Relationship of dietary features related to acid load and subsequent kidney disease: Atherosclerosis Risk in Communities Study; lead author: Casey M. Rebholz

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.c.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.

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. I will be using CMS data in my manuscript _____ Yes x _____ No

References

9. Schwingenschackl L, Hoffmann G: Diet quality as assessed by the Healthy Eating Index, the Alternate Healthy Eating Index, the Dietary Approaches to Stop Hypertension score, and health outcomes: a systematic review and meta-analysis of cohort studies. J Acad Nutr Diet 2015, 115:780-800 e785.


