ARIC Manuscript Proposal # 3098

PC Reviewed: 1/9/18 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Do plant-based diets modulate the risk of chronic kidney disease?

b. Abbreviated Title (Length 26 characters): Plant-based diets and CKD

2. Writing Group:

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

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3. Timeline:

Data analysis, manuscript preparation, and writing will take place over 1.5 year.

4. Rationale:

In the US, 26 million adults have chronic kidney disease (CKD), and more than 600,000 have end-stage renal disease (ESRD), the final stage of CKD which is defined as permanent failure of the kidney which requires renal replacement therapy via dialysis or transplantation.[1] Diabetes and hypertension are the two leading causes of ESRD.[1]Ten percent of those on dialysis die per year,[1] and mortality is remarkably high even among CKD patients who are not dialysis-dependent.[2] Many patients with CKD die of cardiovascular disease (CVD).[3]

Diet is one of the most modifiable risk factors of chronic conditions, including diabetes, hypertension cardiovascular disease, and kidney disease. High consumption of vegetables, fruits and whole grains has been associated with reduced risk of obesity, diabetes, hypertension and coronary heart disease ,[4–6] whereas red or processed meat has been associated with elevated risk.[7,8] Recent studies on sources of dietary protein and CKD risk revealed that plant-based diets which are comprised predominantly of foods of plant origin (vegetables, fruits, nuts, and legumes), and low in animal foods, may be important to consider for prevention of ESRD, and prevention of CKD complications. Systematic reviews have shown that plant-based diets are associated with lower risk of obesity, hypertension, diabetes, and CVD.[9–12] Epidemiological studies found that high consumption of red or processed meat were associated with an increased risk of incident CKD and ESRD,[13,14] whereas nuts and legumes were associated with a decreased risk.[13]

In line with these findings, controlled feeding trials of individuals without diabetes also showed promising results on the effect of plant-based diets on kidney function.[15–17] These trials suggested that a short-term vegetarian diet was associated with a decrease in albumin excretion rate (AER).[15,16] For example, in a 2-week cross-over trial of 10 men, decreasing animal protein intake by increasing plant foods led to a significant reduction in AER.[17] In controlled feeding trials of diabetic patients, plant protein intakes which increased consumption of fiber and phytochemicals showed improved kidney function.[18,19] In a 7-week randomized cross-over trial of patients with type II diabetes, participants showed a decrease in urinary nitrogen, proteinuria, blood sodium, and serum phosphorous when their diets were high in soy protein compared to when their diets were high in animal protein.[20]

However, previous studies observed changes in renal function over a short period of time, and the study populations have mainly consisted of individuals with diabetes. No epidemiological study has assessed the associations between a gradient of overall plant-based diets and the risk of incident kidney disease (CKD, ESRD) in the general population or examined the longitudinal associations between plant-based diets and eGFR trajectories among those with preserved kidney function at baseline. In addition, many previous studies have not differentiated between healthful and less healthful plant foods (i.e., refined grains, sugar-sweetened beverages) within the context of an overall plant-based diet.[21–24]

Thus, we propose to use established plant-based diet indices which provide different scores for animal foods, healthy plant foods, and less healthy plant foods to address these gaps using data from a large cohort study with long-term follow-up.

5. Main Hypothesis/Study Questions:

Aim 1: To investigate how plant-based diets are associated with changes in kidney function (eGFR) over time, and with major risk factors of CKD in the ARIC Study.

Hypothesis 1: Higher adherence to the overall plant-based diets and healthful plant-based diets is associated with slower decline in kidney function (eGFR) over time, and protective for the risk of incident hypertension, diabetes, and obesity, independent of established kidney disease risk factors. Higher adherence to less healthful plant-based diets is associated with faster decline in kidney function over time and higher risk of incident hypertension, diabetes and obesity.

Aim 2: To evaluate the associations between plant-based diets and the risk of incident ESRD and other clinically important end-points including incident CVD and all-cause mortality in the ARIC Study.

Hypothesis 1: Higher adherence to the overall plant-based diets and healthful plant-based diets is associated with lower risk of ESRD, CVD, and all-cause mortality independent of established kidney disease risk factors. Higher adherence to less healthful plant-based diets is associated with higher risk of ESRD, CVD, and all-cause mortality.

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 analyze the association between plant-based diets measured at visit 1 and 3 and changes in kidney function over time (eGFR over 25 years), major risk factors of CKD (incident hypertension, diabetes and obesity), and other clinically important end-points (incident ESRD, CVD, and all-cause mortality).

Inclusion/Exclusion

The proposed study will include men and women with complete information on dietary intake derived from a food frequency questionnaire. Those with 10 or more missing responses on the food frequency questionnaire at visit 1, or implausibly low caloric intake or high caloric intake will be excluded (women: <500 or >3500 kcal; men: <600 or >4500 kcal). Participants with diabetes, cardiovascular disease, cancer, or kidney disease at baseline will be excluded as well.

Dietary Assessment

At visit 1 and visit 3, trained interviewers collected participants' usual intake of foods and beverages in the past year using a 66-item semi-quantitative food frequency questionnaire, a modified version of the Willett/Harvard food frequency questionnaire.[25,26] Visual aids were used to illustrate portion sizes. We will use cumulative average diet, which incorporates dietary intakes that were measured at visit 1 and 3 to improve estimation of usual dietary intakes.[27]

Definition of Plant-Based Diets

We will use the consumption of plant and animal food items as reported on the food frequency questionnaire to calculate an overall plant-based diet index (PDI), healthy plant-based diet index (hPDI), and a less healthy (unhealthy) plant-based diet index (uPDI) using the approach outlined in Satija et al.[12,28] We will categorize each food item into one of 18 food

groups, which are classified as animal foods, healthy plant foods (i.e. fruits, vegetables, whole grains), and less healthful plant foods (i.e. sugar-sweetened beverages, sweets/desserts, potatoes, refined grains). Then, we will calculate quintiles of consumption for each of the 18 food groups and assign a score from 1 to 5. For PDI, in each plant food category, participants in the highest quintile of consumption will receive a score of 5 whereas those in the lowest quintile of consumption will receive a score of 1. Participants will receive a score of 1 for the highest quintile of consumption of animal foods (reverse scores). For hPDI, only the healthful plant foods will receive a score of 5 for the highest quintile of consumption whereas less healthy plant foods and animal foods will receive reverse scores. For uPDI, only the less healthy plant foods will receive positive scores, and healthy plant foods and animal foods will receive reverse scores. All indices range from 18 (lowest possible score) to 90 (highest possible score). All three diet indices will be divided into deciles (ordinal variable) for analyses.

As secondary analyses, *a priori* criteria will be used to define a binary variable of vegetarian diet and an ordinal variable of a spectrum of vegetarian diets using the FFQ administered at baseline and visit 3 to study the association between vegetarian diets and the risk of CKD [vegans as consuming no animal products (red meat, poultry, fish, eggs, milk, and dairy products <1 time/month), lacto-ovo vegetarians as consuming dairy products and/or eggs ≥1 time/month but no fish or meat (red meat, poultry, and fish <1 time/month), pesco-vegetarians as consuming fish ≥1 time/month and dairy products and/or eggs but no red meat or poultry (red meat and poultry <1 time/month), semi-vegetarians as consuming dairy products and/or eggs and meat (red meat and poultry ≥1 time/month and <1 time/week) and non-vegetarians as consuming animal products >1 time/week].[22]

Outcome Ascertainment

Changes in eGFR over time: Serum creatinine that was collected at visit 1, visit 2, visit 4, and visit 5 using the modified kinetic Jaffe method.[29] Estimated glomerular filtration rate (eGFR) based on serum creatinine and cystatin will be calculated by the 2009 Chronic Kidney Disease Epidemiology Collaboration equation.[30] eGFR (mL/min) will be analyzed as a continuous variable. For those who develop ESRD, we will impute an eGFR value of 15 mL/min/1.73 m^2 to address informative censoring.

Incident hypertension: Three blood pressure measurements using a random-zero sphygmomanometer were taken by a certified technician, and the second and third measurements were averaged. We will define incident hypertension as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90mmHg or antihypertensive medication use.

Incident Diabetes: Incident diabetes will be defined as the following: self-reported diagnosis of diabetes, diabetes medication use, fasting blood glucose measurement of ≥126mg/dL, or nonfasting glucose measurement of ≥200mg/dL.

Obesity: BMI (kg/m^2) will be derived from measured height (cm) and weight (kg) of the participants. Obesity will be defined as those with BMI ≥30 kg/m^2.

Incident ESRD: Incident ESRD will be defined as the initiation of renal replacement therapy (transplantation or dialysis) through linkages with the US Renal Data System registry from baseline to December 31, 2012.[31]

Incident CVD: Incident CVD will be defined as a composite outcome including stroke, coronary heart disease, and heart failure.[32] ARIC staff identified incident CVD through active surveillance on cardiovascular disease-related hospitalizations and deaths. Incident stroke and coronary heart disease were adjudicated by a group of experts.

All-cause mortality: Vital status was identified through annual follow-up phone calls, hospital discharge records, newspaper obituaries, state death records, and the National Death Index.[33] All-cause mortality will be defined as death from any cause.

Statistical analyses

We will examine baseline characteristics of the study population according to deciles of plant-based diet indices. To test for differences by deciles, we will use chi-square tests for categorical variables and linear regression for continuous variables. We will also estimate the incidence of hypertension, diabetes, obesity, ESRD, CVD and all-cause mortality stratified by five diet groups.

To explore the association between plant-based diets and kidney function over time, we will use linear mixed models with a random intercept and slope. A variable representing the subject mean and variables representing interactions with time and indicator variables of deciles of plant-based diet scores will be used to examine longitudinal changes over time. Covariates to be adjusted are: sex, race-center (white, black), age (continuous), smoking status (current smoker, former smoker, never smoker), physical activity (physical activity score), socioeconomic status (education), alcohol intake, total energy intake, medication use (i.e., lipid-lowering, antihypertensive, diabetes medication use).

To evaluate the association between plant-based diet indices and major risk factors of CKD, we will use Cox proportional hazards models using time to event or censoring (death or end of follow-up) as the time metric. The same set of covariates as above will be adjusted. For ESRD, CVD, and all-cause mortality, additional covariates including baseline BMI, history of hypertension, and baseline kidney function will be adjusted. Next, we will conduct stratified analyses by sex and race-center to evaluate if the association between plant-based diets and the outcomes of interests are constant across strata.

Then, if there is an association between plant-based diets and ESRD, CVD, and all-cause mortality, we will explore mediation analyses to examine the extent to which the associations between plant-based diets and these clinical end-points are mediated by hypertension, diabetes, and obesity. We will include each risk factor separately in the final model and assess whether hazard ratios are attenuated after its inclusion. If hazard ratios are attenuated more than 15%, then these risk factors may explain the association between plant-based diets and clinical end points.

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)?

Dietary intake is related to risk of developing elevated or high blood pressure in middle-aged adults: ARIC (ARIC Manuscript Proposal #1208). Lead author: Lyn M. Steffen

Associations of plant-and animal-based food consumption with risk of developing type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. Lead author: Lyn M. Steffen

Influence of food intake patterns on incidence of CHD and stroke and all-cause mortality: ARIC (ARIC Manuscript proposal #750). Lead author: Aaron Folsom

Weng LC, Steffen LM, Szklo M, Nettleton J, Chambless L, Folsom AR. A diet pattern with more dairy and nuts, but less meat is related to lower risk of developing hypertension in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) study. *Nutrients*. 2013 May 21;5(5):1719-33.

These manuscript proposals did not evaluate the association between different types of plant-based diets and kidney disease outcomes. We invited Lyn Steffen, the lead author and co-author of these previous manuscript proposals and manuscript to be a coauthor on the present manuscript proposal. We found no overlap between other proposals.

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.

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.

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