1.a. Full Title:
Foods, dietary patterns, and prevalence of microalbuminuria in the Atherosclerosis, Plaque and CVD in Communities Study

1.b. Abbreviated Title:
Foods, dietary patterns, and microalbuminuria

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

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3. Timeline:
Data preparation and analysis will begin upon approval, and manuscript drafting will commence once suitable analytical models are finalized.
Initial drafts will be circulated among the writing group members within four months of proposal approval.

4. Background & Rationale:
Urinary excretion of albumin occurs as a result of altered permeability of the renal glomerular membrane and, thus, is considered a marker of kidney damage, predicting further dysfunction and development of overt kidney disease. “Microalbuminuria” is defined as a level of urinary albumin that is elevated, but still within the range of “normal” total urinary protein. In addition to indicating renal damage, it is also hypothesized that microalbuminuria reflects endothelial dysfunction and atherosclerosis in other vascular beds, including the carotid arteries and retinal vasculature.
Urinary albumin levels are particularly relevant in persons with diabetes and hypertension, signifying target organ damage as a result of the pathogenesis of those diseases. Population-based studies also show that non-diabetic persons with microalbuminuria have increased risk of CVD independent of gender, age, hypertension, and other cardiovascular disease risk factors. Interestingly data show that even small increases in urinary albumin translate into increased risk of CVD, suggesting that urinary albumin excretion is among a constellation of factors that reflect an underlying process (or processes) that increases risk.
Because of the reported associations between albuminuria and subsequent risk of CVD, it is important to identify lifestyle factors that reduce risk of microalbuminuria. It is hypothesized that dietary intake, and particularly protein intake, increases the work load of the kidney, and subsequently may contribute to compromised kidney function and urinary albumin excretion. Observational studies have mainly focused on macronutrient intake in persons with diabetes, although a more recent study expanded its investigation to also include micronutrients in a diabetes-free population. Some of these studies have found that greater protein intake, particularly from animal sources, is positively associated with risk of microalbuminuria. Although not all studies have found positive association between protein intake and albuminuria, most studies have not differentiated animal vs. plant protein sources. Several small randomized interventions in persons with diabetes have noted an adverse effect of red meat, in particular, on kidney function and urinary albumin excretion. In these small trials, replacement of red meat with alternative protein sources (vegetable protein, chicken, or fish) significantly reduced renal hyperfiltration and urinary albumin excretion. Similarly, a case-control study in persons with type I diabetes found that fish consumption was associated with lower risk of microalbuminuria.

Overall, the strongest hypothesis appears to be for dietary protein (dependent on source) to influence urinary albumin excretion, but the association between other aspects of diet and albuminuria have yet to be fully elucidated, especially in persons without diabetes. Although investigating the roles of various nutrients is important, such findings do not always easily translate to real-world application. Nutrient synergy within, and among, foods could have additional effects on kidney dysfunction and damage, beyond that noted for nutrients alone. Indeed, other studies support the role of foods or dietary patterns in relation to factors associated with risk of microalbuminuria, such as blood pressure and endothelial function. However, very few studies have evaluated associations between urinary albumin excretion and foods or food consumption patterns.

Therefore we propose to evaluate the relation between diet—particularly dietary patterns and food sources of protein (animal vs. plant sources)—and prevalence of microalbuminuria in the Atherosclerosis, Plaque and CVD in Communities Study.

(see page 5 for references)

5. Hypotheses:

1a) Total animal protein and food sources of animal protein, especially red meat, will be positively associated with prevalence of microalbuminuria and the ratio of urinary albumin:creatinine.

1b) Total plant protein and food sources of plant protein will be inversely associated, with prevalence of microalbuminuria and the ratio of urinary albumin:creatinine.

2a) Empirically-derived and a priori defined dietary patterns, each reflecting high consumption of animal products (high in cholesterol and saturated fat and low in micronutrients and fiber), will be positively associated with prevalence of microalbuminuria (dichotomous variable, ≥250 mg/g) and the ratio of urinary albumin:creatinine (continuous variable).

2b) Contrasting empirically-derived and a priori defined dietary patterns, each reflecting high consumption of plant foods (high in micronutrients, fiber, and polyunsaturated fats), will be inversely associated with prevalence of microalbuminuria and the ratio of urinary albumin:creatinine.
6. Data:

* **LONGITUDINAL ANALYSIS**: Associations between dietary data collected at baseline and exam 3 and urinary albumin:creatinine ratio derived from the 4th clinical exam (main Atherosclerosis Risk in Communities Study)

* **CROSS-SECTIONAL ANALYSIS**: Associations between dietary data collected during 2005-6 and urinary albumin:creatinine ratio derived from 2005-6 clinical exam (Atherosclerosis, Plaque and CVD in Communities Study)
  - *In this cross-sectional study we will also evaluate models that use previous measures of diet, i.e., the mean each baseline, exam 3, and exam 5 reported dietary intakes.*
  - *In the cross-sectional study we will conduct supplementary analyses that use the mean of exam 4 and exam 5 A/kC as our outcome.*

**EXCLUSIONS:**
- Macroalbuminuria (albumin:creatinine ratio ≥250 mg/g)
- Non-white/non-African American (longitudinal analysis); Non-white (cross-sectional analysis)
- Inadequate/unreliable dietary intake information (based on number of unanswered questions on the food frequency questionnaire and extreme kcal intakes)
- In the cross-sectional study, we will also exclude the following:
  - Prevalent type I or II diabetes
  - Prevalent cardiovascular disease
  - Kidney dysfunction (eGFR <60) (or other reported kidney disease)
* These conditions will not be excluded in the longitudinal study, but rather analyses will be stratified by each condition, and formal tests for interaction conducted where appropriate.

**EXPOSURES VARIABLES:**
- Total animal protein intake
  - Food group sources of animal protein (red or processed meat, dairy [high-fat and low-fat each evaluated separately], poultry, fish)
- Total plant protein intake
  - Food group sources of plant protein (fruits, vegetables, nuts/legumes, grains [whole & refined each evaluated separately])
- A priori defined dietary pattern scores reflecting balance between animal and plant foods (higher score = hypothesized ‘healthier’ or plant-based intake)
  - Quartiles of red or processed meat, poultry, fish, and dairy will be weighted according to the following point scale: Qt1 = 3 pts, Qt2 = 2 pts, Qt3 = 1 pt, Qt4 = 0 pts.
  - Quartiles of fruits, vegetables, nuts/legumes, and grains will be weighted according to the following point scale: Qt1 = 0 pts, Qt2 = 1 pts, Qt3 = 2 pt, Qt4 = 3 pts.
  - Score range 0 – 24 pts
  - An alternative score will also be calculated that includes specifically only high-fat dairy (negative) and whole grain (positive) food groups
- Principal Components derived ‘Western’ and ‘Prudent’ dietary patterns
  - Note: previous data from the ARIC population shows that these dietary patterns generally reflect animal-based (Western) and plant-based (Prudent) patterns of consumption. The exception to this generality is that the Prudent dietary pattern does also reflect greater fish intake.
* Intakes of protein, food groups, and dietary pattern scores will be modeled as population-dependent categorical variables and also as continuous variables (as a supplementary test of the robustness of data)
In the cross-sectional study, we will also explore analyses that rank order participants according to quartiles of intake at all 3 exams, i.e., sum of dietary exposure quartile ranks at exam 1, 3, and 5.

Diet is notoriously measured with error. We will explore the effects of bias due to this error. If we feel the degree of bias is large, we will explore methods to correct for some degree of the error in reported dietary intake.

**Outcome Variables:**
- Microalbuminuria defined as urinary Albumin:Creatinine ratio (A/kC) of 25 – 249 mg/g \(^{40}\) (with appropriate correction factor for race and gender\(^ {41}\)) vs. A/kC < 25 mg/g
- Albumin:Creatinine ratio (A/kC as a continuous variable with natural log transformation to correct for skewness)

**Statistical Analysis:**
Data on prevalence of microalbuminuria will be analyzed using logistic regression (SAS 9.1, PROC LOGISTIC). Odds ratios will be calculated according to population-dependent categories of dietary exposure variables (animal/plant protein intake, food group intake, dietary patterns) using the lowest category as the referent. Tests for linear trend will be calculated with the original continuous variable. When exposures are modeled as continuous variables, odds ratios will represent a 1 g/d difference in protein intake, a 1 serving/d difference in food group intake, or a 1 unit difference in dietary pattern score. Because of the graded relation between levels of urinary albumin and overall CVD risk \(^{20,21}\), linear regression will also be used to assess associations between these dietary exposures and (ln)A/kC.

**Confounders/Model Covariates:**
- **Model 1.** Include the following covariates: age, gender, race (in longitudinal analyses only), MN or MD center, energy intake
- **Model 2.** Add the following covariates: education level, physical activity level, smoking (status and cigarette years), alcohol intake, regular multivitamin use,
  - **Model 2b.** Include other food groups in food group analyses; Include other nutrients (e.g., fat, carbohydrate, fiber) in animal protein/vegetable protein analyses
  - *Include potential mediating variables…*
  - **Model 3a.** Add body mass index (BMI) and/or waist circumference
  - **Model 3b.** Add fasting glucose and insulin
  - **Model 3c.** Add systolic blood pressure & use of hypertension medication use
  - **Model 4.** Including all variables listed above
- For the cross-sectional study models will be weighted according to IMT sampling stratum.

**Testing Potential Interactions:**
Interaction between dietary exposures and the variables listed below will be tested in the fully adjusted model before adding potential pathway intermediates (model 2) by including cross product terms. Stratified analyses will be presented if odds ratios appreciably differ.
- sex, race (in longitudinal analysis only), BMI, hypertension status
- CVD, diabetes, low eGFR—as described previously for longitudinal analysis only

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

8.a. Will the DNA data be used in this manuscript? No
8.b. NA
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. There is no overlap between this proposal and current proposals/published manuscripts.

10. What are the most related manuscript proposals in ARIC?
1123 Albuminuria and kidney function as predictors of cardiovascular events mortality
   Lead Author: Astor B
1012 Association between cardiovascular risk factors and albuminuria in the ARIC study
   Lead Author: Hsu CC

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use any ancillary study data? No
11.b. NA

12. 1-3 year completion expectation: 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.

REFERENCES


