1. Title:
Dietary Risk factors for decreased renal function in the ARIC study

2. Writing Group:
To be determined: coordinating center contact and other interested ARIC investigators

3. Timeline:
The data for these analyses are already available as part of ARIC visits 1 & 2. We project that the analyses and writing will take place over the next two years.

4. Rationale:
ARIC provides an excellent opportunity to study risk factors for the early stages of the decline in renal function using the visit 1 and visit 2 plasma creatinine measures adjusted for lean body mass (see manuscript proposal title Risk factors for decreased renal function in the ARIC study for justification).

The proposed study will be divided into two analyses. A cross-sectional analysis of risk factors for elevated creatinine during the 3 years of follow-up. In each analysis an estimated creatinine clearance will be constructed after accounting for the estimated lean body mass. This estimated creatinine clearance will be used as the dependent variable in the regression analysis. Each analysis will also be done using logistic regression with binary definition (yes/no) of decreased renal function (elevated creatinine) or declining renal function (rise in serum creatinine larger than the expected laboratory plus physiologic variation). These parallel analytic approaches will ensure that results are robust to the specific statistical model used.

Dietary Protein: For more than 20 years it has been known that patients with renal disease who consume a diet severely restricted in protein have fewer uremic symptoms than those on a normal diet. The relationship of dietary protein and renal disease has been explored in many studies of subjects with advanced renal disease including the recently completed Modification of Diet in Renal Disease (MDRD) trial. It is thought that a low protein diet may decrease the progression of renal disease. However, no clear consensus exists and very little data is available on healthy populations. Study of the relationship between dietary protein intake and serum creatinine is complicated by the fact that meat products contain creatinine. Therefore, meat intake may account for a rise in plasma inferences which can be drawn from the cross-sectional analysis. However, the prospective analysis should yield valid inferences since it is unlikely that an increase in the plasma creatinine of subjects with a high protein diet is due to further increases in their dietary protein. Protein intake will be adjusted for total calorie intake.

Antioxidant Intake: Given the role of inflammatory cells in progressive glomerulosclerosis it is possible that a higher antioxidant intake (diet plus supplements) may protect against the oxidative component of the inflammatory damage caused by these cells. Therefore, the possibility of a protective role for antioxidants on the kidney after adjustment for dietary protein and calorie intake will be explored. Given the preliminary
nature of this hypothesis both lipid soluble antioxidants (vitamin E and beta-carotene), and water soluble antioxidants (vitamin C) will be studied.

Other dietary factors including cholesterol, linoleic acid, calcium and phosphorous will be explored as potential risk factors.

Potential confounding by age, gender, race & socioeconomic factors, blood pressure, hypertension, diabetes, and lipids will be controlled for. All analyses will be done stratified on diabetes, gender, hypertension, and race to avoid overlooking potential interactions.

Subjects who report being on a special diet other than for weight loss, low salt, low cholesterol, weight gain, or diabetes will be excluded from this analysis (Dietary Intake Form Q81 answer F = other). Subjects with a plasma creatinine above 2.0 mg/dl will be excluded as well since they may have been told to restrict their protein intake if their marked renal insufficiency has been diagnosed.

5. Main Hypothesis/Issues to be Addressed:
High protein intake is a risk factor for the decline in renal function.

Low antioxidant intake is a risk factor for the presence of as well as progression of decreased renal function after controlling for protein and caloric intake.

6. Data Requirements:
Data analysis will be performed by Dr. J. Coresh at Johns Hopkins School of Hygiene & Public Health in collaboration with Drs. J. Nieto and T. Shimakawa.
Variables needed: plasma creatinine and time of collection, center, age, gender, race, blood pressure, anthropometric data, dietary data, dietary antioxidants, lipids, lipoproteins and apolipoproteins, medical history data (diabetes), risk factor questions (smoking, alcohol consumption).