ARIC Manuscript Proposal # 1012

PC Reviewed: 05/06/04	**Status: A**	**Priority: 2**
SC Reviewed: 05/07/04	**Status: A**	**Priority: 2**

1.a. Full Title: Association between Cardiovascular Risk Factors and Albuminuria in the ARIC Study

b. Abbreviated Title (Length 26 characters): Albuminuria Risk Factors

2. Writing Group (list individual with lead responsibility first):

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Coordinating center contact - To be determined

3. Timeline:

Determination of microalbuminuria from all visit 4 urine samples (N=11,526) is being performed by the laboratory of Michael Steffes (Univ. of Minnesota). The first process batch (N=6,288 participants) consisting of all of Jackson, MS and Washington Co., MD and diabetic participants from Forsyth Co., NC and Minneapolis, MN has been completed. Samples from the remaining non-diabetic participants from Forsyth Co., NC and Minneapolis, MN (N=5,238 participants) are scheduled to be completed by the end of May 2004 and will be included in the analysis. The remaining data for these analyses are already available as part of ARIC. We project that the analyses and writing will take place over the six months following completion of urinalysis.

4. Rationale:

Renal disease is a growing epidemic in the United States. The incidence and prevalence of ESRD have doubled in the past 10 years and this increase is expected to continue(1). Diabetic nephropathy (DN) is the single most common type of renal disease in new dialysis patients and accounts for more than 1/3 of all patients with ESRD(2-4). The proportion of incident dialysis patients with DN as their primary diagnosis is also increasing dramatically, from 33% in 1990 to 43% in 1998(2). Hypertension is the second most common cause of renal failure and was the primary diagnosis in 26.4% of incident dialysis patients from 1995-99(5). A population particularly affected by kidney disease due to diabetes and hypertension is the U.S. African-American population, which has 3 times the incidence rate of U.S. whites(3).

Microalbuminuria (MA) is the earliest clinical manifestation of DN and refers to an increase in albumin excretion rate (AER) above 30 mg/day and below 300mg/day in a 24-hour urine sample(4). Macroalbuminuria is defined as an albumin excretion above 300 mg/day. In an untimed urine sample (such as the ARIC visit 4 samples), an albumin-to-creatinine ratio (ACR) can be calculated that closely approximates albumin excretion in a 24-hour urine sample (6;7). Individuals with MA have been shown to have increased risk of cardiovascular events (8-12) regardless of diabetic status (13) and to be at increased risk for renal disease progression in those with type 1 diabetes (14;15) and type 2 diabetes(16). Additionally, there is evidence that even high-normal albuminuria may be associated with an adverse cardiovascular risk profile (17). Furthermore, there has been some evidence that the association with microalbuminuria of hypertension may be effect modified by C-reactive protein (18) and also by diabetes (19). In a population with type 1 diabetes, urinary albumin excretion rate was also associated with progression of carotid intima-media thickness (20).

It has been estimated that the prevalence of MA in the U.S. population is 7.8%; in diabetics it is 28.8%, and in hypertensives it is 16.0%(21). MA was associated with older age, African-American and Mexican-American ethnicity, presence of diabetes, hypertension, and elevated serum creatinine concentration(21). Recently, Murtaugh et al. in the Coronary Artery Risk Development in Young Adults (CARDIA) Study demonstrated that prevalent micro- and macroalbuminuria was associated with blood pressure levels not regarded as hypertensive in both Caucasians and African-Americans; additionally, blood pressure measured up to 15 years prior to urinalysis was predictive of microalbuminuric status (22). MA is of particular public health and clinical significance and necessitates more effort to understand its etiology and consequences, especially among high-risk populations. Recently, in the NHANES III population, microalbuminuria was shown to be associated with the metabolic syndrome (defined as the presence of 3 or more of the following risk factors: elevated blood pressure, low high-density lipoprotein cholesterol level, high triglyceride level, elevated glucose level, and abdominal obesity)(23). Though hyperglycemia and hypertension are risk factors for the development of nephropathy, much regarding microalbuminuria is still unknown.

5. Main Hypothesis/Study Questions:

To examine the relationships of cardiovascular risk factors and urinary albumin excretion and nephropathy in ARIC. Specifically, a cross-sectional study of prevalent micro- and macroalbuminuria will be performed examining: 1) associations with visit 4 cardiovascular risk factor profiles; 2) changes (absolute, relative, and rates of change) of risk factor profiles from baseline to visit 4; 3) associations with inflammatory risk factors at baseline and at visit 4, 4) associations with both pathology of small (retinal arteriole-to-venule ratio) and large vessels (carotid intima-media thickness), and 5) associations with the metabolic syndrome.

6. Data (variables, time window, source, inclusions/exclusions):

Data analysis will be performed by C. Hsu at the Johns Hopkins School of Hygiene & Public Health.

Variables needed (available at JHU): serum creatinine and time of collection, center, age, gender, race, blood pressure, physical activity, medication use, alcohol and cigarette use, lipid profiles, inflammatory markers, blood glucose, insulin, anthropometric data, retinal arteriole-to-venule

ratios, carotid intima-media thickness, medical history data (diabetes and cardiovascular events) and hospitalization for cardiovascular disease, and ACRs from visit 4 urines.

ARIC provides an excellent opportunity to study risk factors for nephropathy using the visit 4 stored urines to determine albuminuric status. However, the subset for our analysis is less than the original cohort. Of the original 15,792 participants at baseline, albumin-to-creatinine ratios from visit 4 urines will be available for 11,526 participants (73%). Compared to our sample, the 4,266 participants not included in our analyses are older (age at baseline 54.9y(SD 5.9) vs. 53.9 (SD 5.7)), have more males (46.6% vs. 44.2%), more African-Americans (39.9% vs. 22.3%), more diabetics at baseline (19.4% vs. 9.2%), and had more baseline hypertension (45.7% vs. 31.1%). Approximately 2000 diabetics and 2200 African-Americans are included in our sample.

Methods for measuring urinary albumin(μg) and creatinine(mg) have been described previously and will be performed by Mike Steffes at the University of Minnesota (10). The primary outcome will be defined as micro- or macroalbuminuria. Sex-specific cutpoints will be chosen to delineate normoalbuminuria from microalbuminuria: 17 μg albumin/mg creatinine for men and 25 μg/mg for women. The upper boundary delineating microalbumunira from overt proteinuria will be 250 μg/mg for men and 355 μg/mg for women(24). The sex-specific cutpoints have been shown to correspond well with AER-based definitions of microalbuminuria(24). We will examine case definitions of 1) micro- and macroalbuminuria and also 2) only macroalbuminuria in order to increase specificity. To further increase specificity, we will limit analyses to individuals with estimated GFR>90 at baseline and examine a combined case definition of both decreased renal function (GFR<60) and albuminuria at visit 4.

The availability of serum creatinine and anthropometric measures at visits 1, 2, and 4 provide estimates of the glomerular filtration rate over the course of follow-up. GFR will be estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation (1;25). By examining the relationship between estimated GFR and microalbuminuria, we can better understand how changes in kidney function relate to kidney damage. Additionally, the relationship between albuminuria and systemic vascular damage is unclear. With longitudinal measures of carotid intima-media thickness in addition to measures of renal function and visit 3 retinal photographs, ARIC would allow us to better understand the degree to which microalbuminuria may be a marker of both kidney damage and small and large vessel vascular pathology. Additionally, we can examine the associations with microalbuminuria of the metabolic syndrome cross-sectionally at visit 4 and from visit 1. We can determine which components of the metabolic syndrome across time have the strongest associations with prevalent microalbuminuria. Additionally, the longitudinal nature of ARIC provides an opportunity to examine microalbuminuria among both prevalent and incident diabetics, those with evidence of atherosclerosis, those with evidence of inflammation, hypertensives, and those with dyslipidemia. In baseline diabetics, we can determine how incident versus prevalent hypertension affects microalbuminuria at visit 4; similar analyses can also be performed in baseline hypertensives to tease apart the association of diabetes and hypertension with microalbuminuria. Changes (absolute, relative, and rates of change) of blood pressure, lipid levels, inflammatory markers, blood glucose, carotid intima-media thickness, and physical activity from baseline to visit 4 can be examined in association with prevalent microalbuminuria. We will examine the associations of blood pressure with microalbuminuria (stratified by quartiles of inflammation) to examine possible effect modification by inflammation, which has been demonstrated previously(18). Additionally, high-normal levels of blood pressure compared

to optimal levels of blood pressure can be examined with regard to microalbuminuria. Furthermore, to better understand the relationship between albuminuria, atherosclerosis and cardiovascular risk factors affecting small and large blood vessels, we will also examine if risk factor associations with albuminuria are indicative of solely renal manifestations of disease or of more systemic atherosclerosis and subclinical cardiovascular disease by also examining associations with those with albuminuria, retinopathy, and/or carotid intima-media thickness.

The proposed study will be divided into two analyses. A cross-sectional analysis of risk factors associated with albuminuria at visit 4 and a separate analysis with a longitudinal component examining changes in risk factor profiles prior to visit 4. Variables of interest include blood pressure, diabetes and blood glucose, insulin, serum creatinine and estimated renal function, carotid intima-media thickness, retinal arteriole-to-venule ratios, inflammatory markers, lipids, medication use, and lifestyle risk factors including alcohol and cigarette use. The albumin-to-creatinine ratio will be analyzed as both a continuous variable and a dichotomous (at least microalbuminuria yes/no) outcome. Mean and percentile values for the distributions of urinary ACR will be computed for each gender, age group, and ethnic group. Prevalence of microalbuminuria and macroalbuminuria will be calculated by gender, age group, ethnic group, diabetic and hypertensive status and for specific subpopulations of special interest. We will include potential confounders in our multivariate analyses. Simple and multivariate linear regression will be used to determine urinary ACR relationships to the demographic, health status, and risk factor variables. Simple and multivariate logistic regression will be performed to examine associations with the presence of microalbuminuria and/or macroalbuminuria. Based on the literature, inflammation and diabetes are effect modifiers of the association of blood pressure and microalbuminuria(18;19). Risk associations of blood pressure and microalbuminuria will be stratified by diabetic status and also by quartiles of inflammatory markers. The significance of interaction terms will be tested with the likelihood ratio test.

As a second analysis, we will also examine the association of decline in renal function with subsequent albuminuria. We will examine how urinary albumin excretion is associated with the outcome of chronic kidney disease (CKD) progression, a combined incidence of a rise of at least 0.4 mg/dL in plasma creatinine above baseline (after accounting for laboratory differences between visit 4 and prior visits) or a hospitalization for kidney disease, which has worked well in prior ARIC analyses(26;27).

7.a. Will the data be used for non-CVD analysis in this manuscript? __ **Yes** __✓__ **No**

b. If Yes, is the author aware that the file ICTDER02 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 ICTDER02 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** __✓__ **No**

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 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://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

__✓__ 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)?**

MS#223 Risk factors for decreased renal function in the ARIC Study

11. **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.**

Reference List

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