

ARIC Manuscript Proposal # 1451

PC Reviewed: 11/11/08
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title:

b. Abbreviated Title (Length 26 characters): Race/ethnic differences in diabetes mortality and cardiovascular risk: The Atherosclerosis Risk in Communities (ARIC) Study

2. Writing Group:

Writing group members: Elizabeth Selvin; Hong Zhu; Josef Coresh; Frederick Brancati; others welcome

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

First author: Elizabeth Selvin, PhD, MPH
Assistant Professor of Epidemiology & Medicine
Welch Center for Prevention, Epidemiology and Clinical Research and the
Johns Hopkins Bloomberg School of Public Health
2024 E. Monument Street, Suite 2-600
Baltimore MD 21287

Phone: 410-614-3752
E-mail: lselvin@jhsph.edu

Fax: 410-955-0476

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: Josef Coresh
Address:

Phone:
E-mail:

Fax:

3. Timeline: the proposed project is an analysis of existing data; we anticipate it will take 6 months to 1 year from acceptance of proposal to submission of manuscript to ARIC Publications Committee.

4. Rationale:

Racial/ethnic disparities in cardiovascular mortality in the United States are well established. Blacks are at an increased risk of dying from cardiovascular causes compared to their white counterparts, in large part due to higher mortality following incident myocardial infarction (1;2) and a higher prevalence of hypertension and diabetes (3). Much of the excess risk of developing diabetes in blacks is thought to be attributable to factors such as adiposity and blood pressure (4;5). However, less is known about the role of race/ethnicity on major complications among persons with a diagnosis of diabetes. Among individuals with diagnosed diabetes, blacks are significantly more likely to develop retinopathy (6;7), kidney disease (8-10), and have higher rates of amputation (11) compared to their white counterparts. There are surprisingly few studies regarding cardiovascular complications and total mortality. In fact, from what data do exist, there is no evidence of an increased risk of the development of cardiovascular disease among blacks in the setting of diabetes. The Chicago Heart Association Detection Project in Industry Study found that white men with diabetes had more than twice the mortality risk as their black counterparts even after adjustment for age and other cardiovascular risk factors (HR 2.51, 95% CI 2.08 to 3.02). In the Multiple Risk Factor Intervention Trial (MRFIT), no statistically significant difference in age-, income-, and risk factor-adjusted cardiovascular mortality was observed comparing blacks taking medication for diabetes to similar whites (HR 0.88, 95% CI 0.71 to 1.09). Other studies examining racial differences in use of cardiovascular procedures suggests profound racial disparities, with blacks significantly less likely to undergo cardiovascular procedures compared to whites with similar risk factor profiles and disease severity (12;13). It is unclear if this holds true in the setting of diabetes.

Ultimately, in adults with diabetes in the U.S., race/ethnic differences in risk of cardiovascular morbidity, cardiovascular mortality, and total mortality are not well characterized.

5. Main Hypothesis/Study Questions:

The objective of this proposal is to examine potential race/ethnic differences in total, cardiovascular, and non-cardiovascular mortality and incident cardiovascular disease in persons with diabetes in the ARIC cohort. Under the assumption that associations may differ by definition of incident cardiovascular disease, we propose to compare the relative risk estimates across varying definitions of incident cardiovascular events (e.g., silent MI detected at visit, fatal MI/CHD, fatal stroke, fatal CHD, and cardiac procedures).

Hypothesis 1: Black-white differences in cardiovascular risk will differ depending on the outcome definition used, for example with whites more likely than blacks to have cardiac procedures. The existing literature suggests that overall cardiovascular incidence and mortality in persons with diabetes does not differ by black-white race/ethnicity after adjustment for cardiovascular risk factors.

Hypothesis 2: Glycemia (HbA1c and fasting glucose levels), diabetes medication use, smoking, physical activity, income, socioeconomic status, insurance status, and having a usual source of care may partially or wholly explain any observed black-white differences in cardiovascular morbidity and mortality in persons with diabetes.

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: Prospective cohort study with Visit 2 as baseline (the only visit for which HbA1c data are available)

Exposure: Race/ethnicity, black vs white

Outcomes: incident total cardiovascular disease (coronary heart disease or stroke), total, cardiovascular and non-cardiovascular mortality occurring after Visit 2 through 2005 (or most current follow-up available). In defining cardiovascular incidence, we will examine separately the individual end points of silent MI, non-fatal MI, fatal MI/CHD, fatal/non-fatal stroke, and cardiac procedures.

Covariates: Age, sex, waist circumference, BMI, LDL-, HDL- and total cholesterol, triglycerides, systolic and diastolic blood pressures, blood pressure medication use, body mass index, smoking, Baeke physical activity score, education level, income, diabetes medication use, hemoglobin A1c, health insurance status, usual source of care

Sensitivity analyses: we will evaluate whether any racial differences are consistent across age, gender, BMI, and education subgroups. We will also conduct analyses using different definitions of diabetes (undiagnosed, diagnosed).

Exclusions: non-African American and non-white, and participants missing covariates of interest.

Diabetes will be defined primarily by a self-reported physician diagnosis of diabetes. We will also assess risk in those persons with undiagnosed diabetes defined by a single fasting glucose measurement greater than or equal to 126 mg/dl or a non-fasting glucose greater than or equal to 200 mg/dl.

Main analyses: time-to-event models (Cox proportional hazards) to compare the risk of cardiovascular disease and total mortality in blacks vs white participants with diabetes after adjusting for covariates of interest. We will confirm proportionality of the hazard functions.

Major limitations: In the interpretation of the results, we will not be able to separate out the effects of geography from race/ethnicity as geographic location (center) and race/ethnic status overlap extensively in the ARIC study (~90% of blacks were recruited from Jackson). Even with adjustment for rigorously measured known risk factors for diabetes and cardiovascular risk factors, we will also not be able to rule out the possibility of residual confounding. Race/ethnicity is a multifaceted marker of complex social and cultural processes which we may not be able to fully capture in these data.

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 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 ICTDER03 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 ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? Yes No

8.c. If yes, is the author aware that some DNA data is not allowed to be used by 'for profit' groups. Is this data being used by a 'for profit' organization? If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded? 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.csc.c.unc.edu/ARIC/search.php>

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#123 White AD, "Sex and race differences in short-term prognosis after acute coronary heart disease events: the Atherosclerosis Risk in Communities (ARIC) Study"

MS# 167 Brancati FL, "Incident type 2 diabetes mellitus in a community-based biracial cohort: The Atherosclerosis Risk in Communities Study"

MS#252 Brancati, FL "Correlates of prevalent diabetes by race"

MS# 230 Krop, JS "A community-based study of explanatory factors for the excess risk for early renal function decline in blacks vs whites with diabetes: The Atherosclerosis Risk in Communities Study"

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes No

11.b. If yes, is the proposal
 A. primarily the result of an ancillary study (list number* 2003.05)
 B. primarily based on A/RIC 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/>

12. 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.

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Reference List

- (1) White AD, Rosamond WD, Chambless LE, Thomas N, Conwill D, Cooper LS et al. Sex and race differences in short-term prognosis after acute coronary heart disease events: the Atherosclerosis Risk In Communities (ARIC) study. *Am Heart J* 1999; 138(3 Pt 1):540-548.
- (2) Ding J, ez Roux AV, Nieto FJ, McNamara RL, Hetmanski JB, Taylor HA et al. Racial disparity in long-term mortality rate after hospitalization for myocardial infarction: the Atherosclerosis Risk in Communities study. *American Heart Journal* 2003; 146(3):459-464.
- (3) Carnethon MR, Lynch EB, Dyer AR, Lloyd-Jones DM, Wang R, Garside DB et al. Comparison of Risk Factors for Cardiovascular Mortality in Black and White Adults. *Archives of Internal Medicine* 2006; 166(11):1196-1202.
- (4) Brancati FL, Kao WHL, Folsom AR, Watson RL, Szklo M. Incident Type 2 Diabetes Mellitus in African American and White Adults: The Atherosclerosis Risk in Communities Study. *JAMA: The Journal of the American Medical Association* 2000; 283(17):2253-2259.
- (5) Resnick HE, Valsania P, Halter JB, Lin X. Differential effects of BMI on diabetes risk among black and white Americans. *Diabetes Care* 1998; 21(11):1828-1835.
- (6) Harris MI, Klein R, Cowie CC, Rowland M, Byrd-Holt DD. Is the risk of diabetic retinopathy greater in non-Hispanic blacks and Mexican Americans than in non-Hispanic whites with type 2 diabetes? A U.S. population study. *Diabetes Care* 1998; 21(8):1230-1235.
- (7) Harris EL, Sherman SH, Georgopoulos A. Black-white differences in risk of developing retinopathy among individuals with type 2 diabetes. *Diabetes Care* 1999; 22(5):779-783.
- (8) Brancati FL, Whittle JC, Whelton PK, Seidler AJ, Klag MJ. The excess incidence of diabetic end-stage renal disease among blacks. A population-based study of potential explanatory factors. *JAMA* 1992; 268(21):3079-3084.
- (9) Krop JS, Coresh J, Chambless LE, Shahar E, Watson RL, Szklo M et al. A Community-Based Study of Explanatory Factors for the Excess Risk for Early Renal Function Decline in Blacks vs Whites With Diabetes: The Atherosclerosis Risk in Communities Study. *Archives of Internal Medicine* 1999; 159(15):1777-1783.
- (10) Cowie CC, Port FK, Wolfe RA, Savage PJ, Moll PP, Hawthorne VM. Disparities in incidence of diabetic end-stage renal disease according to race and type of diabetes. *N Engl J Med* 1989; 321(16):1074-1079.

- (11) Resnick HE, Valsania P, Phillips CL. Diabetes Mellitus and Nontraumatic Lower Extremity Amputation in Black and White Americans: The National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, 1971-1992. *Archives of Internal Medicine* 1999; 159(20):2470-2475.
- (12) Ferguson JA, Tierney WM, Westmoreland GR, Mamlin LA, Segar DS, Eckert GJ et al. Examination of racial differences in management of cardiovascular disease. *J Am Coll Cardiol* 1997; 30(7):1707-1713.
- (13) Kressin NR, Petersen LA. Racial Differences in the Use of Invasive Cardiovascular Procedures: Review of the Literature and Prescription for Future Research. *Ann Intern Med* 2001; 135(5):352-366.