

ARIC Manuscript Proposal #2740

PC Reviewed: 4/12/16
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Sex differences in the association of diabetes with cardiovascular disease outcomes among African Americans in the Atherosclerosis Risk in Communities Study (ARIC) prospective cohort: 1987-2013

b. Abbreviated Title (Length 26 characters): CVD risk in blacks by sex

2. Writing Group:

Writing group members: Kristen M. George, Aaron R. Folsom, Liz Selvin, Jim Pankow, B. Gwen Windham

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

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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).

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3. Timeline: Begin analysis following ARIC committee approval

4. Rationale:

An estimated 9.3% of the United States population has diabetes mellitus, primarily type 2 diabetes, and the prevalence is expected to continue increasing.¹ Diabetes is an established risk factor for cardiovascular disease (CVD), the leading cause of morbidity and mortality among people with diabetes.² Further, diabetes is considered a coronary heart disease risk equivalent.³ While women are at reduced absolute risk of a CVD event compared to men of similar age, this advantage is lost among women with diabetes compared to men with diabetes.⁴

Sex differences in the association of diabetes with CVD outcomes have been studied comprehensively in whites, however, further study is needed to examine these differences among minority populations for whom the disease burden is particularly high.¹ Specifically, incidence and prevalence of diabetes is higher among African Americans, particularly African American women, than whites.⁵⁻⁶ A previous study has also suggested that some of the excess risk in African Americans is accounted for by modifiable risk factors, especially in African American women compared to white women.⁶ However, little is known about the within sex differences on the association between diabetes and incident CVD among African Americans and whether these differences mirror what has been seen among whites. And, to our knowledge there has been no study testing the interaction of sex with diabetes in relation to CVD outcomes in African Americans, as pointed out in a recent review.⁴ The Atherosclerosis Risk in Communities Study (ARIC) offers an opportunity to examine CVD outcomes among African American men and women to determine whether sex and diabetes interact to affect CVD incidence, mirroring what has been seen consistently in studies of sex-diabetes interactions among whites.

References:

- (1) *National diabetes statistics report: estimates of diabetes and its burden in the United States*. Atlanta, GA: Centers for Disease Control and Prevention; 2014.
- (2) Matheus AS de M, Tannus LRM, Cobas RA, et al. Impact of diabetes on cardiovascular disease: an update. *Int J Hypertens*. 2013; 2013: 1-15.
- (3) National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report. *Circulation* 2002; 106: 3143-3421.

- (4) Regensteiner JG, Golden S, Huebschmann AG, et al. Sex differences in the cardiovascular consequences of diabetes mellitus: a scientific statement from the American Heart Association. *Circulation*. 2015; 132: 2424-2447.
- (5) Carter JS, Pugh JA, and Monterrosa A. Non-insulin-dependent diabetes mellitus in minorities in the United States. *Annals of Internal Medicine*. 1996; 125(3): 221-232.
- (6) Brancati FL, Kao W, Folsom AR, Watson RL, Szklo M. Incident Type 2 Diabetes Mellitus in African American and White Adults: The Atherosclerosis Risk in Communities Study. *JAMA*. 2000;283(17): 2253-2259.

5. Main Hypothesis/Study Questions:

We hypothesize that there is an additive sex by diabetes interaction for CVD incidence among African Americans in the ARIC cohort. That is, the absolute risk of CVD associated with diabetes will be greater in women than men, or alternatively, the joint risk of CVD for women with diabetes is greater than expected risk based on an additive risk model. The CVD outcomes will include incident coronary heart disease (CHD), stroke, peripheral vascular disease (PVD), and heart failure. For comparison, we will verify that the interaction is present for whites in ARIC as well.

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).

Design: prospective from visit 1 with CVD events through 2013 or most recent data available.

Exclusions: all participants who are not African American or white, those missing information on diabetes status at baseline, and those with prevalent CHD, total stroke, PVD, or heart failure at baseline.

Exposures: sex and diabetes (defined as non-fasting blood glucose \geq 200 mg/dL, fasting blood glucose \geq 126 mg/dL, self-report of diabetes, or reporting taking medication for diabetes or high blood sugar)

Outcomes: incident CHD (events and deaths), total stroke, PVD (hospitalization for lower extremity revascularization during follow-up or ABI < 0.90), and heart failure (hospital ICD codes)

Analysis: Poisson regression will be used to calculate incidence rates of CVD outcomes in African Americans, stratified by sex and diabetes status from visit 1, 1987-89, through 2013. Sensitivity analyses will be conducted to assess the impact of including diabetes self-report, CHD revascularization, and stroke subtypes. Race-specific competing risks Cox proportional hazards will be used with diabetes as a time dependent variable to assess hazard of CVD outcomes over the same time period, with special emphasis on testing the additive sex by diabetes interaction using relative excess risk (RERI) as well as the multiplicative interaction. Hazard ratios will be calculated for women with diabetes, men with diabetes, men without diabetes, with the reference group being women without diabetes. Associations between diabetes and CVD by sex among whites will also be examined to assess whether sex differences examined in previous studies persist. Models will be adjusted for age, center, systolic blood pressure and hypertensive medication, LDL and HDL cholesterol body mass index (BMI), kidney function, physical activity, alcohol use, tobacco use, and education.

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.csc.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)?

There are many manuscripts on diabetes and CVD outcomes. We have included the main leads on these papers over the past 25 years (Folsom, Selvin, Pankow) to ensure we avoided overlap.

Adeniyi A, Folsom AR, Brancati FL, et al. Incidence and risk factors for cardiovascular disease in African Americans with diabetes: the Atherosclerosis Risk in Communities (ARIC) study. *J Natl Med Assoc.* 2002; 94(12): 1025-1035.

Folsom AR, Chambless LE, Duncan BB, et al. Prediction of coronary heart disease in middle-aged adults with diabetes. *Diabetes Care.* 2003; 26(10): 2777-2784.

Folsom AR, Rasmussen ML, Chambless LE, et al. Prospective associations of fasting insulin, body fat distribution, and diabetes with risk of ischemic stroke. The Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Diabetes Care.* 1999; 22(7): 1077-1083.

Folsom AR, Szklo M, Stevens J, et al. A prospective study of coronary heartdisease in relation to fasting insulin, glucose, and diabetes. The Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care.* 1997; 20(6): 935-942.

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* _____)

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.csc.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.csc.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 No.