ARIC Manuscript Proposal # 1494

PC Reviewed: 04/14/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Blood pressure and the development of glucose disorders: the ARIC Study, CARDIA Study, and Framingham Heart Study

b. Abbreviated Title (Length 26 characters): BP and incident glucose disorders

2. Writing Group: Gina S. Wei, Sean Coady; Frederick Brancati; Elizabeth Selvin, Caroline Fox; David C. Goff; Daniel Levy; Vasan Ramachandran

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _GW_ **[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: Analysis will be done over the next few months with the goal of submitting an abstract to AHA Epi Council Meeting (Spring 2010) and submitting the paper to a journal shortly thereafter.

4. Rationale: Diabetes and hypertension share several common pathophysiological pathways. Markers of endothelial dysfunction are associated with new-onset diabetes(1;2), while endothelial dysfunction is associated with elevated blood

pressure(3). Low-grade systemic inflammation has also been shown to occur both in hypertension and type 2 diabetes(4-8). Metabolic syndrome, which includes elevated blood pressure as one of its components, is a well-known risk factor for developing type 2 diabetes(9). Some diabetes prediction rules have found blood pressure, along with other metabolic traits, as a major prediction variable(10;11). But whether and the extent by which blood pressure by itself (independent of metabolic abnormalities) is associated with increased risk for diabetes and pre-diabetes deserves further investigation.

In a longitudinal study of men only (Johns Hopkins Precursors Study), elevated blood pressure was an antecedent of new onset type 2 diabetes in middle age by 20-25 years (12). The study was limited by relying on self report to determine diabetes. Lipid levels, baseline blood glucose levels, and several other predictors of diabetes were unavailable. Recently the Women's Health Study found that among healthy middle-aged women (mean age: 54 years), baseline blood pressure (and progression of blood pressure) strongly predicted incident diabetes(13). The relationship remained even with baseline BMI-stratified analyses and accounting for other potential confounders. However, the use of self-report for blood pressure levels was a limitation. Lipid and BMI levels were also based on self report. Furthermore, the study lacked data on baseline fasting glucose, a known predictor of incident diabetes.

In ARIC, Gress et al. found that baseline hypertension independently predicted incident diabetes and that this relationship largely explained the apparent relationship between antihypertensive treatment and diabetes risk (14). This paper, however, did not investigate blood pressure quantitatively and did not seek to determine threshold or other aspects of the risk relationship.

Together, the ARIC study, CARDIA (Coronary Artery Risk Development in Young Adults) study, and the Framingham Heart Study provide a rich dataset to study whether elevated blood pressure is an independent risk for developing glucose disorders (new onset diabetes, impaired fasting glucose, and impaired glucose tolerance). Data on both men and women will allow for gender comparisons; data on Blacks and Whites will allow for racial comparisons. Carefully measured data on blood pressure and glucose levels, as well as on important co-variates such as baseline glucose, BMI, and lipid levels, are available. Finally, blood pressure medications are also available to examine their potential confounding effects on incident diabetes.

Reference List

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(11) Wilson PWF, Meigs JB, Sullivan L, Fox CS, Nathan DM, D'Agostino RB, Sr. Prediction of Incident Diabetes Mellitus in Middle-aged Adults: The Framingham Offspring Study. *Arch Intern Med* 2007; 167(10):1068-1074.

(12) Golden SH, Wang NY, Klag MJ, Meoni LA, Brancati FL. Blood pressure in young adulthood and the risk of type 2 diabetes in middle age. *Diabetes Care* 2003; 26(4):1110-1115.

(13) Conen D, Ridker PM, Mora S, Buring JE, Glynn RJ. Blood pressure and risk of developing type 2 diabetes mellitus: The Women's Health Study. *Eur Heart J* 2007; 28(23):2937-2943.

(14) Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. *N Engl J Med* 2000; 342(13):905-912.

5. Main Hypothesis/Study Questions:

Elevated blood pressure is a clinical predictor for developing new-onset diabetes and pre-diabetes (impaired fasting glucose and impaired glucose intolerance) independent of other clinical factors, including metabolic abnormalities.

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).

Inclusion: ≤ 55 years old at the ARIC Cohort Exam 1 (1987-89). Exclusion: free of diabetes at baseline and returned for at least one follow-up exam. Analytic Plan:

Incidence rates for diabetes by sex, age, and race will be calculated using standard person-years methods and according to blood pressure categories at baseline. The association of blood pressure with incident diabetes and pre-diabetes (impaired fasting glucose and, if data available, impaired glucose tolerance) will be evaluated in standard Cox-proportional hazards models adjusting for age, race, sex and baseline blood pressure. Separate models will examine the association after further adjustment of covariates [including baseline fasting glucose levels, waist circumference, lipid levels, smoking status, and family history of diabetes (if available), education, income, and physical activity; classes of antihypertensives], as well as stratified by baseline blood pressure and BMI categories. Consideration will be given to account for the relationship between metabolic syndrome and incident diabetes (e.g. for sensitivity analysis, to consider excluding those with more than one of the three metabolic syndrome components at baseline). The proportional hazards assumption will be checked using the method of Grambsch and Therneau. Additional models will evaluate the association of blood pressure and incident diabetes and pre-diabetes using longitudinal measures of blood pressure and BMI in time-dependent Cox models. Blood pressure as both a continuous and categorical (normal, prehypertension, and hypertension) variable will be utilized.

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 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 _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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
____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.cscc.unc.edu/ARIC/search.php

__X___ 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)?

This specific topic has not been previously proposed in ARIC. Some potentially related proposals in ARIC are listed here. Dr. Brancati, the ARIC co-author for our paper, is a co-author on 2 of these proposals:

1. "*Association between family history of type 2 Diabetes Mellitus, the multiple metabolic syndrome (MMS), and the risk of developing type 2 diabetes mellitus*"
- Relatedness to our paper: We plan to use family history of diabetes a co-variate.

2. "*Does Anti-Hypertensive Therapy Predispose to Development of Diabetes Mellitus?*" -
- Relatedness to our paper: We plan to use classes of blood pressure medications a co-variate

3. "*Prediction of diabetes mellitus and impaired glucose tolerance in middle-aged adults: The Atherosclerosis Risk in Communities Study"*
- Relatedness to our paper: The lower age range of our cohort is 35 years old (those <45 years old. will come from CARDIA and the Framingham Heart Study); thus, it is not limited to middle-aged. Instead of generating a predication rule for diabetes, we will focus only on elevated blood pressure as the primary predictor of new onset diabetes.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes _X__ 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.cscc.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.