ARIC Manuscript Proposal # 1431

PC Reviewed: 10/14/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Hemoglobin A1c, glucose, and incident diabetes: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): HbA1c and incident diabetes

2. Writing Group:
Writing group members: Elizabeth Selvin, Michael Steffes, Hong Zhu, Ciprian Crainiceanu, Lynne Wagenknecht, James Pankow, Frederick L. Brancati, Josef Coresh, 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]**

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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: We expect all HbA1c assays to be complete by ~November 2008. Analyses will be initiated once all data are cleaned. We aim to have this manuscript submitted to the ARIC publications committee in <6 months from this date.

4. Rationale:

Previous studies have investigated the relation between fasting glucose and incident diabetes (1-3), including a recent study which showed that higher fasting plasma glucose levels in the normal range constitute an independent risk factor for type 2 diabetes among young men (4). The relation of hemoglobin A1c (HbA1c)—a measure of chronic hyperglycemia—and diabetes risk is less well characterized. There is ongoing debate regarding the adoption of HbA1c alone or in combination with fasting glucose for the screening and/or diagnosis of diabetes. Previous studies of the accuracy of HbA1c for the detection of diabetes have largely focused on the ability of HbA1c to identify fasting glucose-defined prevalent diabetes cases (5-7). Data regarding the utility of non-diabetic HbA1c—alone or in combination with fasting glucose—for the prediction of incident diabetes is sparse.

The relationships between glycemia and diabetic complications, like most risk factor-disease relations, exist along a continuum, but there is a need to establish cut-points in clinical practice for decision-making (i.e., when to diagnose or treat). Using data from the ARIC Study, we propose to characterize and compare the continuous dose-response relationships between HbA_{1c} and glucose concentrations and incident diabetes. We will also formally assess the possible presence of threshold effects in this association.

5. Main Hypothesis/Study Questions:

Aim: To determine the association between HbA1c and glucose concentrations at baseline and progression to diabetes mellitus, as determined by fasting glucose, 2-hour glucose, reported physician diagnosis, and medication use. Aim 1 will employ statistical techniques to evaluate thresholds for screening of diabetes using HbA1c and fasting glucose alone and in combination.

The goal of these analyses will be to assess possible categories of HbA1c (alone and in combination with glucose) in the normal range relevant for identifying persons at high risk for clinical outcomes.

> **Hypothesis:** it will be possible to use fasting glucose and HbA1c to identify thresholds (cut-points) that will identify persons at high risk for clinical outcomes and that will be relevant for clinical practice.

Design & Methods

Study design: We will examine the prospective association between baseline (Visit 2) HbA_{1c} and fasting glucose levels—separately and in combination—and incident diabetes. We will directly compare the associations of HbA1c and glucose levels for the prediction of incident diabetes. Visit 2 which took place from 1990-1992 and is the only visit for which stored whole blood samples are available for measurement for HbA_{1c} will be the baseline for all analyses. Glucose measurements are available on all participants at each ARIC examination.

Exposures: HbA1c, glucose

Covariates: Age, sex, race/center, waist circumference, BMI, total, LDL- and HDL-cholesterol, systolic and diastolic blood pressures, blood pressure medication use, triglycerides, smoking, family history of diabetes, Baeke physical activity score (Visit 1), education level (Visit 1)

Outcome: incident diabetes occurring after Visit 2. We will compare definitions based on glucose alone, self-reported diabetes/medication use alone, and glucose and report in combination. We will also assess the association with diabetes defined by an OGTT (available only at visit 4). The ARIC Coordinating Center has developed a time-to-diabetes variable based on glucose values obtained at each ARIC clinical examination (8). The date of onset of diabetes is estimated by linear interpolation using fasting glucose values at the ascertaining visit and the previous one. The glucose level at ascertainment for subjects who had been told they had diabetes or who were on diabetes medication(s) may have been affected by their knowledge of their diabetes status (and in some cases is <126 mg/dl). For these subjects, the time to reach 126 mg/dl was estimated using their fasting glucose level at the earlier visit and a slope estimated using information from all diabetic subjects who had been unaware of their diabetes status. We will conduct additional analyses utilizing self-reported diabetes from annual follow-up phone calls with data available through 2004 (or most recent data available).

Exclusions: participants with diagnosed diabetes at baseline defined by a self-reported physician diagnosis or diabetes medication use, participants with undiagnosed diabetes based on glucose alone, and participants missing HbA1c or covariates of interest.

Statistical Analysis: Adjusted hazard ratios and their 95% CIs for the time to development of diabetes will be computed using Cox proportional hazards models, where time of diabetes is imputed using the derived incident diabetes variable described above. These models will be compared with logistic models using data on diabetes from Visit 3 and 4 without linear extrapolation of glucose levels (time-to-diabetes unknown). We will use penalized smoothing splines (P-splines) (9;10) to characterize and compare the shape of the functions of HbA_{1c} and glucose concentrations and diabetes risk. We will also use parametric and semi-parametric techniques, including recursive cubic spline models (11) to examine possible thresholds or inflection points in the relationship between HbA_{1c}, glucose and incident 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).

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 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.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)?

ARIC-HbA1cV2-200305	1011	Stability of haemoglobin A1c (HbA1c) measurements from frozen whole blood samples stored for over a decade.	Selvin, E
ARIC	1024	Glycemic control and coronary heart disease risk in persons with and without diabetes: The Atherosclerosis Risk in Communities Study	Selvin, E
ARIC	1025	Glycemic control, Atherosclerosis, and risk factors for cardiovascular disease in individuals with diabetes: The ARIC Study	Selvin, E
ARIC	1056	HbA1c and peripheral arterial disease in diabetes	Selvin, E
ARIC	1067	Glycemia (haemoglobin A1c) and incident stroke: The ARIC Study	Selvin, E
ARIC	1031	Empirical validation of the metabolic syndrome components and cutpoints through the prediction of CHD and diabetes using partitioning methods	McNeill, AM
ARIC	1052	Increased risk of type 2 diabetes from a family history of coronary heart disease and type 2 diabetes.	Yeung, E
ARIC	1087	Prediction of incident diabetes: validating risk stratification and prioritzation algorithms using recursive partionong.	Bang, H
ARIC	1164	Hemoglobin A1c as a Risk Factor for Heart Failure Hospitalization among Persons with Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study	Pazin Filho, A
ARIC	167	Incident type 2 diabetes mellitus in a community-based biracial cohort: The	Brancati, FL

		Atherosclerosis Risk in Communities Study	
ARIC	474	Alocohol consumption and the risk of type 2 diabetes mellitus: Atherosclerosis Risk in Communities Study	Kao, WH
ARIC	539	Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities Study): a cohort study	Schmidt,
ARIC	668	Delayed Diagnosis of Incident Type 2 Diabetes Mellitus in the ARIC Study	Samuels, A.
ARIC	682	TNFa, IL-6 and incident diabetes mellitus	Schmidt, MI
ARIC	770	Depressive symptoms and the risk of type 2 diabetes: the Atherosclerosis Risk in Communities study	Golden, SH

Schmidt MI, Duncan BB, Bang H, Pankow J, Ballantyne C, Golden S, Folsom A, Chambless L. Predicting High Risk for the Development of Diabetes—The Atherosclerosis Risk in Communities Study. Diabetes Care, 2005; 28: 2013-2018.

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

11.b. If yes, is the proposal

_X__ A. primarily the result of an ancillary study (list number* _2003.05 *and* 2006.15 _)

___ 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. ES

Reference List

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(2) Knowler WC, Pettitt DJ, Savage PJ, Bennett PH. Diabetes incidence in Pima indians: contributions of obesity and parental diabetes. *Am J Epidemiol* 1981; 113(2):144-156.

(3) Ferrannini E, Nannipieri M, Williams K, Gonzales C, Haffner SM, Stern MP. Mode of Onset of Type 2 Diabetes from Normal or Impaired Glucose Tolerance. *Diabetes* 2004; 53(1):160-165.

(4) Tirosh A, Shai I, Tekes-Manova D, Israeli E, Pereg D, Shochat T et al. Normal Fasting Plasma Glucose Levels and Type 2 Diabetes in Young Men. *N Engl J Med* 2005; 353(14):1454-1462.

(5) Buell C, Kermah D, Davidson MB. Utility of A1C for Diabetes Screening in the 1999 2004 NHANES Population. *Diabetes Care* 2007; 30(9):2233-2235.

(6) Saudek CD, Herman WH, Sacks DB, Bergenstal RM, Edelman D, Davidson MB. A New Look at Screening and Diagnosing Diabetes Mellitus. *J Clin Endocrinol Metab* 2008; 93(7):2447-2453.

(7) Davidson MB, Schriger DL, Peters AL, Lorber B. Relationship Between Fasting Plasma Glucose and Glycosylated Hemoglobin: Potential for False-Positive Diagnoses of Type 2 Diabetes Using New Diagnostic Criteria. *JAMA: The Journal of the American Medical Association* 1999; 281(13):1203-1210.

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(9) Ruppert D, Wand MP, Carroll RJ. Semiparametric regression. Cambridge: Cambridge University Press, 2003.

(10) Marsh L, Cormier DR. Spline regression models. no. 07-137 ed. Thousand Oaks, Calif: Sage Publications, 2001.

(11) Harrell FE. Regression modeling strategies
with applications to linear models, logistic regression, and survival analysis. New York: Springer, 2001.