ARIC Manuscript Proposal # 808

PC Reviewed: 07/03/01	**Status: __A__**	**Priority: __2__**
SC Reviewed: 07/05/01	**Status: __A__**	**Priority: __2__**

1.a. Full Title: Prediction of diabetes mellitus and impaired glucose tolerance in middle-aged adults: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Predicting diabetes/IGT

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

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3. Timeline:

After approval, the initial analyses and writing will take place between July and December of 2001, final analyses by April, 2002, final writing and submission of manuscript between April and June 2002.

4. Rationale:

Type II DM is a leading cause of morbidity and mortality in the United States raising concerns about how to prevent effectively its associated burden of disease. Tertiary prevention has been advocated for various complications, including macrovascular disease(1). Secondary prevention based on universal DM screening is not currently recommended by ADA, although selective screening is advocated for individuals at high risk, identified by a combination of risk factors for diabetes(2). The strategy of identifying high risk individuals has gained relevance also for the primary prevention of DM as recent studies documented the feasibility of preventing diabetes by lifestyle interventions in individuals with IGT(3)(4). Additionally, prevention of DM was also accomplished with the use of ACE inhibitors(5)(6). These strategies require that diabetes be either diagnosed, screened for or predicted.

Different from thromboembolic events such as myocardial infarction or stroke, where extensive analysis of cohort studies(7)(8) permits estimation of an individual's probability of a clinical event, little work has been done to develop and evaluate clinical prediction rules for detecting subclinical diabetes mellitus or a high risk state for diabetes in adults.

CDC researchers have developed a rule for predicting prevalent diabetes, adopted by ADA in 2000, based on family history, physical activity, age and obesity, as well as being a member of a high risk minority group(9). The San Antonio Heart Study developed predictive risk equations, highlighting the ability of such equations to predict risk of diabetes at least as well as the state of impaired glucose tolerance(10).

The ARIC study, currently evaluating predictive equations for incident CHD (Chambless, 5th International Conference abstract), and having an incident diabetes cohort with over 1200 new cases, is ideally poised to investigate questions related to diabetes risk. Additionally, its large numbers of African-American individuals may allow the development of ethnicity specific prediction rules. One potential limitation to the ARIC database is the use of a 75g OGTT only at 9 year follow up. However, although this challenge test remains the diagnostic gold standard, the simplicity of the fasting glucose in clinical and population screening settings has led the ADA to establish it as the main screening and clinical diagnostic tool for diagnosing diabetes.

In ARIC, diabetes status was ascertained through similar protocols at visits 1 to 4, and defined as a fasting glucose $\geq$7.0 mmol/L ($\geq$126 mg/dL), a non-fasting glucose $\geq$11.1 mmol/L (200mg/dL), a self-reported history of either treatment for diabetes or physician-diagnosed diabetes. Additionally, at Visit 4, a standard 75g oral glucose tolerance test was performed, with diabetes being ascertained if 2h postload glucose was $\geq$ 11.1 mmol/l.

5. Main Study Questions:

(1) Development of clinical prediction rule to estimate 10 year risk of incident diabetes based on Visit 1 clinical presentation (age, gender, ethnicity, family history of diabetes, hypertension, smoking status, BMI, WHR) alone or supplemented with Visit 1 basic laboratory tests (HDL-C, triglycerides, insulin, WBC, fasting glucose).

(2) Development of a clinical prediction rule to estimate the probability, among those without previous diagnosis of DM, of having DM or IFG (at Visit 1) on the basis of clinical presentation (age, gender, ethnicity, family history of diabetes, hypertension, smoking status, BMI, WHR) alone or supplemented with basic laboratory tests (HDL-C, triglycerides).

(3) Development of a clinical prediction rule to estimate the probability, among those not having diabetes by fasting glucose, of having diabetes or IGT by OGTT. This rule will use data on fasting glucose and clinical presentation (age, gender, ethnicity, family history of diabetes, hypertension, smoking status, BMI, WHR), alone or supplemented with other basic laboratory tests (HDL-C, triglycerides, insulin). The reason for this objective is that postprandial glycemia has been suggested to be more predictive than fasting glucose of cardiovascular events and death (11; 12), leading the ADA to currently reassess the necessity of an oral glucose tolerance test for those negative for diabetes on the basis of fasting glucose alone.

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

(1) Diabetes status: DM, as defined above, at visits 1-4, and component variables.
(2) Demographic variables: age, gender, ethnicity

(3) Other diabetes risk factors at visit 1: BMI, WHR, hypertension status, systolic and diastolic BP, family history of diabetes, HDL-cholesterol, triglycerides, wbc, cigarette smoking status, hypertensive medications
(4) Other diabetes risk factors at visit 4 (for objective 3): BMI, WHR, hypertension status, systolic and diastolic BP, family history of diabetes, HDL-cholesterol, triglycerides, cigarette smoking status, hypertensive medications
(5) Exclusion criteria: Exclude persons who did not return to a follow-up visit, whose race is neither black nor white, and with incomplete information about potential predictors; for objective 1, exclude those with diabetes at baseline or unknown diabetes status at follow-up.
(6) Fasting glucose from FHS to permit evaluation of probability that an individual will have 2 abnormal results on the basis of a single ARIC fasting glucose value.

7. Analysis plan

A. Objective 1
1. The modeling strategy to identify individual probability of developing diabetes will utilize either discrete proportional hazards or Weibull models.
2. Statistically significant gain in predictive ability will be evaluated through testing of change of area of the ROC curve.
3. An issue to be addressed in the results is the estimation of a *clinical* diagnosis of diabetes (which requires, in the absence of symptoms), 2 glycemic determinations, and the ARIC data, which, to be fully used, would use only 1 determination for the ascertainment. One possibility is to estimate, using ARIC and FHS data, the proportion of cases defined as abnormal with one measurement that would be abnormal on both of two measurements. FHS data are included, as this permits evaluation of repeated glucose measures over a shorter time interval than 3 years. This estimate would be less biased, with respect to the presence of any given risk factor, if it were made in a risk factor-adjusted manner.
4. Estimates of diabetes incidence will be presented extrapolated to a 10-year interval.
5. We may also consider the creation of color-coded charts, similar to those developed by Rod Jackson (http://cebm.jr2.ox.ac.uk/docs/prognosis.html#refs), displaying risk on the basis of the presence of major risk factors (age, BMI/WHR/others)

B. Objectives 2 and 3
The analyses related to these objectives will utilize logistic regression of Visit 1 data for objective 2 and Visit 4 data for objective 3.

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 ICTDER01 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 ICTDER01 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 ICTDER01 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

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