ARIC Manuscript Proposal # 1326

PC Reviewed: 01/15/08	**Status: __A__**	**Priority: _2__**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:

Evaluation of the FINDRISC Diabetes Score to Identify Individuals at High Risk for Diabetes among middle-aged Caucasian and African-American individuals in the ARIC Study

b. Abbreviated Title (Length 26 characters):
FINDRISC to predict DM

2. Writing Group:
Writing group members:
Annie McNeill, Cynthia Girman, Jaakko Tuomilehto, Sherita Hill Golden, Wayne Rosamond, Bruce Duncan, Maria Ines Schmidt

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

F**irst author**: Annie McNeill, PhD

Address: Associate Director
Epidemiology, UG1D-60,
PO Box 1000 or 351 N. Sumneytown Pike
North Wales, PA 19454
Direct Phone: 919.240.4154

Phone: 919-240-4154 Fax: 215.616.4259
E-mail: annie_mcneill@merck.com

3. Timeline: Analyses will begin immediately upon approval by the Publications and Steering Committee.

4. Rationale:

The worldwide prevalence of diabetes for all age-groups has been estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030.[1] It is estimated that by 2005, the global prevalence of diabetes will increase 1.2 times in Europe, 1.6 times in North America and almost double in other parts of the world.[2] Diabetes is a serious condition with an estimated 2.9 million excess deaths attributed to it in the year 2000[3]. It is a leading cause of blindness, amputation, renal failure, and neuropathy among adults in the U.S. and the leading cause of death among patients with diabetes — rates of CVD mortality/morbidity are 2-4 times greater among populations with diabetes.[4] In contrast, the risk of CVD among individuals with pre-diabetes (impaired glucose tolerance [IFG] or impaired fasting glucose [IGT]), is only moderately elevated[5] but increases greatly following the onset of frank diabetes.[6] Thus, intervention to prevent or delay the onset of diabetes may also prevent the development of CVD and other complications, although this relationship has not yet been established from existing clinical trials.

Eight large clinical trials[7-14] have shown that the onset of frank diabetes can be prevented or delayed by either lifestyle modification (weight loss/physical activity) or pharmacologic treatment among populations with IGT and/or IFG, with risk reductions ranging from 25-60%[5] over the period of study follow-up. Further, although most of these studies were not designed to evaluate whether the rates of diabetes complications would also be delayed or prevented, two studies[11, 13] reported reduced rate of increase in the intima media wall thickness for patients on pharmacologic treatment compared to placebo and one (STOP-NIDDM)[11] reported a significant beneficial effect of pharmacologic therapy on CVD events relative to placebo.

What many believe to be an epidemic of type 2 diabetes around the world has fueled interest in the development of screening strategies to identify subjects who would benefit from aggressive lifestyle or pharmacologic prevention strategies. Several studies have compared the predictive properties of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) either alone, or in combination, to predict type 2 diabetes, [15-17] with variable diabetes incidence rates for each isolated condition, but strongest when

both IFG and IGT are present. Moreover, IGT but not IFG has been repeatedly found to be a risk factor for CVD and all-cause mortality[18-21]

To improve upon the predictive properties of fasting or 2-hour glucose alone, several multivariable models have been published[22-28] that combine measures of glucose disturbances with an array of clinical variables ranging from well-established risk factors for diabetes to those that are more time-consuming or complicated to obtain in usual clinical practice settings (e.g., insulin secretion/insulin resistance index,[28] CRP, insulin sensitivity index[27]). Prediction of diabetes with these clinically "complex" algorithms have been shown in most cases to improve only marginally beyond algorithms composed of fasting or post-prandial glucose measures plus more well-established, and clinically available risk factors for diabetes.[22, 23, 26, 27]

Although such "complex" algorithms may be appropriate for etiologic investigation of the underlying causes of the development of type II diabetes, they may be impractical from the standpoint of public health screening efforts to identify patients at high risk of glucose disturbances who would benefit from aggressive prevention strategies. Further, risk prediction algorithms that require fasting or 2-hour glucose measures[22-26] also limit the contexts in which they can be applied. Poor measurement reliability, cost, and logistical complications associated with performing an oral glucose tolerance test (OGTT) are well documented [29] and the requirement for fasting blood samples for glucose, lipids, or other laboratory-based measures may limit the opportunities for public health screenings for at-risk individuals in non-medical settings.

A number of "simple" diabetes risk scores (FINDRISC [30], ADA [31], Cambridge [32], German Risk Score [33], Rotterdam[34], Inter99[35]) have been developed to screen for prevalent or incident diabetes, based on a combination of age, family history of diabetes, history of gestational diabetes, anthropometric measures (weight, height, BMI, waist circumference), levels of physical activity, dietary habits, use of antihypertensives or corticosteroids, or other variables that do not require laboratory measurements. These scores may be especially useful for identifying patients at risk for diabetes outside of traditional medical care settings. However, these scores have been developed largely in European Caucasian populations, and require external validation in separate cohorts to

establish the generalizability across populations with different race, gender, and age distributions.

Specifically, the FINDRISC risk score[30] was developed using data from the population-based prospective Finnish cardiovascular and diabetes surveys (Finrisk surveys) carried out in 1987 and 1992 with a 10-year and 5-year follow-up, respectively. The development of the algorithm was based on the prerequisite that no blood testing is needed and that an individual can carry out the test without any advice from health personnel. Thus, it includes information obtained directly from the individual, and is thus appropriate for screening in large-scale, non-medical care settings. The algorithm was developed in the Finnish population to screen for individuals at high risk of developing drug-treated diabetes [30] and includes the following measures: age, BMI, waist circumference, history of medication use for hypertension, self-reported history of elevated glucose (or gestational diabetes), physical activity, and daily consumption of fruits and berries. The score has been externally validated to identify subjects at high risk for incident diabetes in a separate Finnish population [30] and to identify prevalent undiagnosed diabetes, impaired fasting glucose, or metabolic syndrome in Finnish[36] and Italian populations.[37] External validation of the FINDRISC in Asian populations is underway *(personal communication with J. Tuomilehto)*. However, performance characteristics of the FINDRISC score in U.S. populations of Caucasian or African-American ethnicity have not been documented.

The purpose of the proposed study is to evaluate the ability of the FINDRISC score (1) to predict incident diabetes (treated or untreated) during 9-years of follow-up; and (2) to identify subjects with prevalent IGT, IFG, and undiagnosed diabetes using cross-sectional data among Caucasian and African-American middle-aged subjects. Although the original FINDRISC score includes measures of physical activity (30 minutes a day on most days) and dietary patterns (fruit and vegetable consumption), developers of algorithm have clarified that neither item added much to the predictive power of the statistical model, but were included in the risk score for public health purposes to emphasize the importance of physical activity and diet in the prevention of diabetes.[30] Thus, the unavailability of these two measures in the ARIC data is not expected to affect the diagnostic properties of the FINDRISC score in this population. A third component that will not be included as part of the modified FINDRISC score is the "history of

diabetes" as ARIC subjects with prevalent diabetes based on physician diagnosis or current use of medication for diabetes at baseline will be excluded from the analysis.

5. Main Hypothesis/Study Questions:

Study Questions:

1. Evaluate the diagnostic properties (ROC, sensitivity, specificity, negative predictive power) of the modified FINDRISC score to predict incident diabetes during 9-yrs of follow-up for the overall population and within race by gender subgroups, in patients with no evidence of diabetes at baseline.

2. Evaluate the diagnostic properties (ROC, sensitivity, specificity, negative predictive power) of the modified FINDRISC score to predict prevalent IGT, IFG, and undiagnosed diabetes among the overall population, and within race by gender subgroups

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).

Objective 1: Prediction of Incident DM using the FINDRISC score

Data from baseline and visits 2, 3, and 4 will be used to ascertain baseline and incident DM status. Baseline data will be used to ascertain subjects' score on the FINDRISC algorithm.

Exclusions: Individuals with the following conditions will be excluded:

<u>At Baseline</u>

- Bloodwork obtained after < 8 hours fasting (subjects with non-fasting blood samples are excluded because baseline diabetes cannot be ascertained)
- Prevalent diabetes (fasting glucose >= 126 mg/dl, self-reported physician diagnosis or use of diabetes medications).
- Race other than African American or White or Black participants not residing in Forsyth or Jackson centers.
- Missing data on available components of FINDRISC, diabetes status or other key variables

<u>At Follow-up visits</u>

- Missing data in variables that precludes ascertainment of incident diabetes status during follow-up

Outcome variable: Incident DM defined as (1) self-report of physician diagnosis, (2) medications for diabetes or (3) FPG≥ 126 at either visit 2, 3, or 4, or 2-hr glucose at visit 4 ≥ 200 mg/dl. (*Note: OGTT was conducted only at visit 4)*

Objective 2: Identification of Prevalent IGT, IFG and undiagnosed diabetes using the FINDRISC score

Data from visit 4 of the ARIC study will be used to identify subjects with prevalent IGT, IFG and undiagnosed diabetes. Data from all visits (baseline, 2, 3, 4) will be used to exclude subjects with diagnosed DM by visit 4.

Exclusions: Individuals with the following conditions will be excluded:

- Blood work obtained after < 8 hours fasting (subjects with nonfasting blood samples are excluded because cannot be categorized in terms of DM, IGT, or IFG outcomes)
- Previously diagnosed diabetes by visit 4: subject self-report of physician diagnosis or current use of medications for diabetes at visit four or at any other previous study visit (baseline, visit 2, or visit 3)
- Race other than African American or White or Black participants not residing in Forsyth or Jackson centers.
- Missing data on available components of FINDRISC at visit 4
- Missing data in variables that precludes ascertainment of a subject's status with regard to diagnosed or undiagnosed diabetes, IFG, or IGT classification

Outcome variables:

- Undiagnosed diabetes defined as fasting glucose ≥ 126 mg/dl or 2-hr glucose ≥ 200 mg/dl
- IGT defined as 2-hour glucose from the OGTT (140-199 mg/dl)
- IFG defined as fasting glucose (100-125 mg/dl)
- IGT or IFG, as defined above

Data Analysis

Logistic regression will be used to evaluate predictive properties of the FINDRISC score to predict cumulative incidence of diabetes over 9-years of follow-up (visit, 2,3, or 4) and to predict prevalent IFG, IGT, or diabetes at visit 4. To investigate the utility of various cutpoints on the score to predict the outcome of interest, ROC curves will be generated by plotting the sensitivity of the score versus the false-positive rate (1-specificity) and threshold levels which appear to give the most robust balance of sensitivity/specificity across the different outcomes and subgroups will be explored. Stratified analyses will be conducted by race and sex subgroups to evaluate the consistency of the predictive properties of the FINDRISC score with African-American and Caucasian men and women. To investigate the degree of improvement in prediction when fasting glucose or other laboratory-based or clinical measures are included (e.g., HDL-C, triglycerides, systolic blood pressure), separate logistic regression models will be fitted to include these variables individually and ROC curves will be compared using a method that accounts for comparisons within the same data (STATA roccomp procedure). Selection of these variables will be based on results that indicate strong bivariate associations between measures routinely collected during medical exams and incident diabetes

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 ICTDER02 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 ICTDER02 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 ICTDER02 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.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)?

Schmidt, M.I., et al., *Detection of undiagnosed diabetes and other hyperglycemia states: the Atherosclerosis Risk in Communities Study.* Diabetes Care, 2003. **26**(5): p. 1338-43.

Schmidt, M.I., et al., *Identifying individuals at high risk for diabetes: The Atherosclerosis Risk in Communities study.* Diabetes Care, 2005. **28**(8): p. 2013-8.

Note: the lead author of these papers is has been invited to be part of the writing group for the current proposal.

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.**

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