ARIC Manuscript Proposal # 1777

PC Reviewed: 4/8/11  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1. a. Full Title:
Modifiable Risk Factors Associated With Progression from Incident Impaired Fasting Glucose to Diabetes Mellitus Type 2: A Pooled Cohort Analysis

b. Abbreviated Title (Length 26 characters):
IFG progression to DM

2. Writing Group:
Writing group members:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. LZ

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3. Timeline:
We will complete a co-authored/approved first draft of the manuscript by June, 2011.

4. Rationale:
The prevalence of diabetes has tripled in the United States since 1980(1) and is a leading cause of morbidity, cardiovascular mortality, and healthcare expenditure(2).
Prediabetes, an intermediate state between normal glycemia and diabetes mellitus type 2 that includes impaired fasting glucose (IFG), affects 79 million people above the age of 20 and 16% of the population aged 12 to 19. Multi-center randomized controlled trials, the Diabetes Prevention Program (DPP) and the Finnish Diabetes Prevention Study, have demonstrated that intensive lifestyle intervention (modifying diet, increasing physical activity, and losing weight) can reduce the incident diabetes in an overweight pre-diabetic population by 58% at 3 years and 30% at ten years. However, these intensive lifestyle interventions are often difficult to implement in real clinical settings.

Other modifiable risk factors for the progression from prediabetes to diabetes should be investigated to elucidate possible alternative preventive clinical interventions.

Rates of progression from incident pre-diabetes to diabetes and the contribution of risk factors to conversion have been studied in older, mostly male, mostly Caucasian cohorts. The Baltimore Study on Aging demonstrated that 25% of 216 subjects with new-onset IFG (110-125 mg/dl) or IGT progressed to diabetes over ten years. In a retrospective study using an HMO database, 11.3% of 5,452 patients converted from IFG (fasting glucose 100-125 mg/dl) to diabetes in 3 years. Other studies have explored risk factors for progression in various national/racial/ethnic groups without necessarily defining new-onset pre-diabetes, and time with pre-diabetes is likely an important risk factor for progression.

We propose to examine the association between modifiable clinical risk factors (body mass index, waist circumference, physical activity, cigarette smoking, alcohol use, depression, HDL, triglycerides, systolic blood pressure, diastolic blood pressure) and progression from incident impaired fasting glucose (IFG: fasting serum glucose level of 100-125 mg/dl) to diabetes mellitus type 2 (defined as fasting glucose >126 mg/dL or current use of hypoglycemic medication or insulin). We will investigate the relative contribution of each modifiable risk factor to the progression from IFG to DM.

Additionally, we hypothesize that certain demographic factors, such as age, modify the effect of modifiable risk factors, potentially through physiological processes related to insulin sensitivity or muscle mass. The DPP demonstrated that lifestyle change was more effective in participants 60-80 years of age because older adults experienced greater gains in physical activity and more sustained weight losses compared with younger patients. It is unclear whether age plays a role in the influence of physical activity on glucose metabolism independent of weight loss. We also hypothesize that male/female sex modifies the effect of modifiable risk factors, potentially through differences in body composition or muscle mass.

To test our hypotheses, we will pool data from multiple existing longitudinal cohort studies so that we will have a substantial number of participants who experience incident IFG and enough follow up time after the incidence of IFG to study progression to type 2 diabetes. In addition to using the Atherosclerosis Risk in Communities (ARIC) study, we will carry out simultaneous analyses in the following studies: Coronary Artery Risk Development in Young Adults (CARDIA), Framingham Offspring Study (FOS), and the Multi-Ethnic Study of Atherosclerosis (MESA). We anticipate that our approach will overcome the limitations of previous analyses carried out in single cohort studies because we will have a larger number of incident IFG events and more follow-up time to determine incident diabetes, thus yielding a more statistically-powerful analysis. The
resulting larger dataset is required so that we can test our secondary hypotheses that age and sex modify the effect of these risk factors on progression to incident diabetes.

5. Main Hypothesis/Study Questions:
Our objective is to identify clinical and behavioral factors associated with the time to development of diabetes mellitus type 2 in a cohort of adults with newly-identified IFG. We hypothesize that BMI, waist circumference, alcohol intake, cigarette smoking, depressive symptoms/negative effect, triglycerides, blood pressure and physical inactivity will be positively associated with shorter time to developing type 2 diabetes, whereas HDL cholesterol will be inversely associated with time to developing incident diabetes.

We will test a secondary hypothesis that age at time of incident IFG and male/female sex modify the association between the risk factors and time to incident diabetes.

6. Design and analysis

Exclusion
- Participants who have impaired fasting glucose or diabetes at baseline

Inclusion:
- Participants who are identified as having IFG during the follow-up examinations for their cohort
- Participants who have at least one additional follow-up examination AFTER identification of IFG

Analysis sample:
The analysis sample is comprised of participants who have incident IFG and at least one opportunity to have diabetes identified during a follow-up examination in their cohort.

Definitions:
Impaired fasting glucose: Impaired fasting serum glucose will be defined according to the American Diabetes Association (ADA) as ≥100mg/dl.
Diabetes: Diabetes mellitus type 2 will be defined according to the 2003 ADA fasting glucose criterion (≥126 mg/dL) or report of oral hypoglycemic mediation or insulin.

Covariates
- Age, sex, race/ethnicity and education will be identified at the baseline examination of each cohort.
- The following health behaviors will be identified at baseline and from the examination closest to when incident IFG is identified (when available): alcohol consumption, smoking status, cigarettes smoked per day, Baecke sport physical activity index.
- Clinical characteristics will be determined at baseline and from the examination closest to when incident IFG is identified (when available): body weight (kg) and height (m), waist circumference, HDL cholesterol, triglycerides, systolic and diastolic blood pressure, depressive symptoms.
Weight change will be calculated as the difference between weight at the time of newly-identified IFG and weight at the time incident diabetes is identified or last examination for those who did not develop diabetes during follow-up.

**Analysis Plan and Methods:**
We will begin by studying the distribution of modifiable baseline (“baseline” referring to the examination where incident IFG is identified) characteristics within cohorts and across cohorts. We will calculate the crude and age-adjusted incident rate of diabetes within cohorts and in the pooled sample. We will test our hypotheses using survival analysis. Prior to modeling, we will investigate whether, in a pooled sample, each of the covariates we will study meet the proportional hazards assumption by plotting log-log survival plots. Once we confirm that the proportional hazards assumption is met, we will carry out a set of models using stratified (with each component cohort in the pooled analysis treated as a strata) Cox Proportional Hazards models to generate hazard ratios and 95% confidence intervals. First, we will test each covariate of interest in relation to time to incident diabetes. Our first multivariable model (Model 1), we will adjust for a set of demographic characteristics (e.g., age, race, sex and education). We will identify a set of covariates that are associated with incident diabetes and are not highly correlated (to avoid multicollinearity) and include them in a multivariable model (Model 2) to test which covariates remain independently associated with the incidence of diabetes.

In addition to using Cox Proportional Hazards models to generate hazard ratios and 95% confidence intervals, we will also use an accelerated failure time (AFT) model. The AFT model treats the logarithm of survival time as the response variable and includes an error term that follows a log-logistic distribution. We selected the AFT model because it permits calculation of the percent “lifespan increase” or “time free from diabetes” with respect to any survival time quintile.

We will also test for statistical interaction 1) between age (defined as above or below age 65 years) and modifiable risk factors for predicting incident diabetes 2) between gender and modifiable risk factors for predicting 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 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

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)?

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)* 2008.13___  
 ___ 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.