ARIC Manuscript Proposal # 883

PC Reviewed: 06/18/02	**Status: __A__**	**Priority: __1__**
SC Reviewed: 06/18/02	**Status: __A__**	**Priority: __1__**

1.a. Full Title: Cardiac Autonomic Function and the Development of Incident Diabetes

b. Abbreviated Title (Length 26 characters): HRV and Incident Diabetes

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

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3. Timeline:

- Analyses to begin immediately
- Abstract submitted to AHA Conference on Epidemiology and Prevention, October 2002
- Manuscript to follow

4. Rationale:

There is ample clinical (1) and cross-sectional epidemiological (2-4) evidence relating diabetes and autonomic nervous system dysfunction. It is generally accepted that hyperglycemia among persons with diabetes causes degradation of the small vessels resulting in central and peripheral autonomic neuropathy. However, recent clinical and animal research suggests that the autonomic nervous system plays an important role in the regulation of glucose and fat metabolism, even in the absence of clinically diagnosed of diabetes (5). Despite published research that cites autonomic nervous system dysfunction as a mechanism to explain the association between psychological factors and incident diabetes (6), no study has demonstrated that autonomic nervous system dysfunction independently predicts the development of diabetes.

Support for the biological plausibility of diabetes as a consequence of autonomic impairment, is provided in animal and clinical studies. Insulin resistance, which commonly precedes the development of diabetes, is associated with impaired autonomic dysfunction as measured by increased heart rate and prolonged QT length (3, 7). Thus, the association between autonomic dysfunction and diabetes may be directly mediated by the effects of insulin. Autonomic innervation of major organs and body systems including the pancreas, liver, and skeletal muscle which are responsible for insulin secretion, glucose production, and glucose metabolism, respectively, represents a complex system whereby autonomic dysfunction can impact metabolism (5, 8, 9). Additional proposed mechanisms, which may also act through insulin, include catecholamine secretion, dietary energy intake, and physical activity (5, 9, 10). These probable

mechanisms provide reasonable justification to examine this temporal association in longitudinal studies of human populations.

This association has not previously been evaluated in epidemiologic studies, likely due, in part, to the lack of available measures of autonomic nervous system function and cross-sectional study designs. The Atherosclerosis Risk in Communities cohort has measures of heart rate variability (HRV) at the baseline examination that can estimate overall autonomic nervous system modulation and the specific contribution from the parasympathetic component. These measures can be related to the development of incident diabetes over follow-up. Previous findings in the ARIC cohort report a relationship between autonomic nervous system dysfunction (estimated by low HRV) and metabolic syndrome components (11, 12) as well as health behaviors such as cigarette smoking, and physical activity (2). To investigate whether there is an independent association between low HRV and incident diabetes, these covariates can be statistically controlled in regression models. Such an investigation can test for the first time whether autonomic nervous system dysfunction is a plausible mechanism for the development of diabetes.

5. Main Hypothesis/Study Questions:

Low heart rate variability (an estimate of cardiac autonomic dysfunction) at baseline is associated with an increased risk of developing incident diabetes over follow-up.

A. Preliminary analyses: We will re-examine the cross-sectional association between fasting glucose, insulin, and diabetes diagnosis and heart rate variability at the baseline examination. While this replicates earlier analyses by Liao (3), we will describe this association in the entire ARIC cohort (earlier analyses were in a sub-sample). This association will shape how the longitudinal analyses are conducted.
B. Primary analyses: We will test whether heart rate variability at baseline is a significant predictor of incident diabetes over follow-up. All analyses will be conducted in persons free of diabetes, but because we anticipate a cross-sectional association between fasting glucose and insulin, we will test the association in persons with varying levels of fasting glucose or insulin resistance (estimated by fasting serum insulin). Subgroups will include: (1) persons with normal glucose levels (glucose <110 mg/dL); (2) impaired glucose tolerance (glucose >=110 and <126 mg/dL); (3) "normal" fasting insulin concentrations defined as baseline fasting serum insulin < 75^{th} percentile.
C. Secondary analyses: We will examine the role of two types of covariates, potential explanatory variables and classic confounders, on any association between heart rate variability and incident diabetes. Potential explanatory variables include metabolic syndrome components such as high blood pressure, central or overall obesity, and dyslipidemia. Covariates that are unlikely to explain an observed association, but are associated with heart rate variability and may themselves predict diabetes include cigarette smoking, physical activity, and dietary energy intake. We will introduce covariates from each of the two classes of variables into multivariable regression models to determine whether and how any previously observed association changes.

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

Inclusions/Exclusions: The analysis population will include all black and white participants without prevalent diabetes who fasted for at least 8 hours at the baseline examination.

Visit 1 variables: *Exposures*: supine heart rate variability indices (R-R interval length, mean heart rate, standard deviation of normal R-R intervals, high-frequency power, total power, low-frequency power). *Covariates*: age, race, study center, education, glucose, insulin, prevalent diabetes, prevalent coronary heart disease, physical activity, smoking status, hypertension, systolic and diastolic blood pressure, HDL, LDL, and total cholesterol, triglycerides, waist circumference, waist/hip ratio, body mass index, total caloric intake.

Visits 2, 3, 4: *Outcome*: incident diabetes (based on the ARIC derived variable of fasting glucose > = 126 mg/dL, non-fasting glucose >=200 mg/dL, diabetes control medications, or a previous physician diagnosis).

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://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

__X___ Yes _____ No

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