

ARIC Manuscript Proposal # 1052r

PC Reviewed: 12/03/04

Status: A

Priority: 2

SC Reviewed: 12/10/04

Status: A

Priority: 2

1.a. Full Title: Family History of Coronary Heart Disease and Incident Type 2 Diabetes

1.b. Abbreviated title: Fam Hx of CHD & Incident T2DM

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

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3. Timeline:

Analysis will begin upon proposal approval using the current ARIC dataset.

4. Rationale:

Individuals with type 2 diabetes are at strong risk of developing cardiovascular complications. As high as 55% of type 2 diabetic persons suffer from coronary heart disease (1) and many studies have found a doubling or more of CHD risk in diabetic individuals. (2, 3) Although many studies have shown that DM precedes and predicts CHD, it is still unclear if diabetes definitively causes CHD. Some evidence suggests the contrary, and risk has been observed to increase even before the onset of diabetes. (4) In 1995, Stern (5) proposed a hypothesis that diabetes and CVD arises from common elements of both conditions. His “common soil” hypothesis suggests that the development of cardiovascular events aggregate in diabetics because the diseases share common risks rather than because diabetes causes cardiovascular events.

Stern based some of his reasoning on the fact that fetal and early life nutritional deficiencies can increase the risk of both diabetes and CVD. (6) Nevertheless, the strongest evidence comes from the increasing knowledge about the metabolic syndrome (i.e. obesity, dyslipidemia, glucose intolerance, etc) which increases the risk of both diseases. Additional research since has given more evidence of the connection. The Nurses Health Study (4) found that CHD risk increases prior to the onset of diabetes. Those who eventually developed diabetes had a higher risk of nonfatal MI (adjusted RR = 3.17) compared to those who remained nondiabetic. The association was stronger among the non-obese (and no association with smoking was found), which is evidence for the genetic component of CVD to independently increase the risk of diabetes. Two other smaller studies have replicated these findings (7, 8) and another study (9) has hypothesized oxidative stress and inflammation to linking the two diseases.

If the common soil hypothesis is true, then the family history of CHD should be associated with an increased risk of type 2 diabetes because there are common genetic

predispositions through the mechanisms of obesity (10-15), hypertension (16), the metabolic syndrome (17), and possibly other novel pathways.

Results from this study will not only add insight into the shared etiology between CHD and type 2 diabetes but may also have significant public health implications. Because family history information reflects both genetic and environment risk factors, a study of family history versus a study of genetic markers may serve as a better predictor of disease. Information from genetic studies remains hard to translate on a clinical level whereas the family history information can be easily collected and used. Lastly, if an association is found independent of a family history of diabetes, it would further increase the clinical significance of the findings and the need for diabetes preventive measures among persons with either family history. We propose, therefore, to investigate the association between the Family Risk Score for CHD and incident type 2 diabetes in the ARIC study.

5. Main Hypothesis/Study Questions:

- a. We hypothesize that the Family Risk Score as well as categorical measures of family history of CVD will be positively associated with diabetes even after adjusting for known risk factors.
- b. The increased risk of incident type 2 diabetes associated with family history of CHD will be present in both individuals with and without a family history of diabetes.

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

Main exposure variable:

Family history will be assessed by number of relatives reported by proband with CVD. Participants reported parental history at baseline and siblings' history at the second visit. The Family Risk Score will also be used to quantify the composite risk based on these reports (from baseline and first follow-up visit at 3 years) and adjusted for expected risk based on the Framingham Risk Score, as described by Pankow et al. (18) ARIC participants from all four sites will be used as inclusion criteria permits. Family Risk Score will be analyzed both as a continuous trait and as a categorical variable (low, medium, and high).

Main Outcome:

Incident type 2 diabetes at visit 2, visit 3, visit 4

Other variables:

Age, gender, race, smoking, alcohol intake, diet, physical activity level, parental history of type 2 diabetes, body mass index (BMI), waist-to-hip ratio (WHR), insulin, glucose, triglycerides, HDL cholesterol, LDL cholesterol, total cholesterol, systolic blood pressure (SBP), diastolic blood pressure (DBP), and inflammatory markers (from baseline and from ancillary study 1995.09).

Exclusions:

- Participants missing family history of CVD data
- Participants missing information on diabetes status
- Participants who were lost to follow-up after their 1st visit
- Participants with prevalent diabetes status at baseline

Analysis:

- 1) Assessment of potential outliers with appropriate transformation of variables to achieve normality.
- 2) Assessment of potential confounders: based on literature review and statistical methods, including chi square for categorical variables and t-tests for continuous and included in statistical models accordingly. We recognize that residual confounding may remain, particularly due to incomplete assessment of family history of diabetes as well as other unmeasured exposures.
- 3) Incidence per 1,000 person-years by categories of family history for unadjusted association between family history and DM
- 4) Cox Proportional Hazards to determine the risk of incident type 2 diabetes comparing those with a family history of CVD and those without (see exposure section). Separate models will be made first adjusting for age, race, and gender, then adjusting for additional confounding behavioral variables (smoking, alcohol consumption, etc), and lastly adjusting for confounding anthropometric and biochemical variables (BMI, WHR, triglycerides, etc). Stratified analysis will be made by family history of diabetes. Interactions between the family CHD risk score and family history of diabetes will be assessed.
- 5) Case-cohort sub-analysis with data on inflammatory markers from Pankow ancillary study on inflammation and the development of diabetes (AS#1995.09).

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes 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 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.csc.unc.edu/ARIC/search.php>

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)?

MS #271 – Pankow: Family Hx & Hemostasis

MS #322 – Pereira (with Pankow co-author): Family CHD History and Lipid Levels

- 11. 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.**

References

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