1.a. **Full Title**: Spousal Diabetes Status as a Risk Factor for Incident Diabetes Over 25 Years: The Atherosclerosis Risk in Communities (ARIC) Study

b. **Abbreviated Title (Length 26 characters)**: Spousal diabetes concordance

2. **Writing Group**:  
   Writing group members: Duke Appiah, Pamela J. Schreiner, Elizabeth Selvin, Ellen W. Demerath, James S. Pankow

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

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3. **Timeline**: A draft will be sent to the coauthors by the end of April 2016 and a final draft will be submitted to the P&P Committee by June 2016

4. **Rationale**:  
Type 2 diabetes (hereafter referred to as diabetes) continues to be a critical public health challenge worldwide. In the United States, more than 29.1 million (9.3%) adults over the age of
20 years are estimated to have diabetes (1). Alarmingy, this number is estimated to increase in the face of the current obesity epidemic.

A family history of diabetes is an important component in diabetes risk assessment. Familial aggregation studies estimate the heritability of diabetes to be approximately 25% (2, 3). However, genetic variants (>65) currently identified by genome-wide association studies to be associated with diabetes explain less than 10% of the disease’s heritability (4), and do not fully explain the rapid rise in diabetes prevalence. While genetic factors are important in the etiology of diabetes, environmental factors such as obesity, diet, and physical activity play a major role in the expression of genetic risk and the incidence of diabetes.

Spouses are usually genetically unrelated but may share some environmental factors. Accordingly, previous studies suggest that spouses of persons with diabetes have a greater risk of diabetes compared to spouses of persons without diabetes (5-9). However, a recent meta-analysis of 5 cross-sectional studies found no significant spousal concordance for diabetes after accounting for body mass index (10). The only prospective study to date (5) reported a 32% greater risk of diabetes among spouses of persons with diabetes but failed to take into account other risk factors for diabetes. Despite diabetes-associated environmental factors observed to differ in various racial/ethnic groups, previous reports have mainly assessed homogeneous populations. Among Americans, spousal concordance of diabetes has been assessed in older (>65 years) adults of Hispanic origin (6), but it is unknown if these results are generalizable to other racial/ethnic groups.

Therefore, we aim to assess, prospectively, spousal concordance (risk of diabetes in the non-diabetes spouse) for diabetes independent of other risk factors among 4,505 spouse pairs (baseline, 1987–1989) in the Atherosclerosis Risk in Communities (ARIC) study, a biracial cohort of white and black men and women

5. Main Hypothesis/Study Questions:

Spouses of persons with diabetes will have a significantly greater risk of developing diabetes independent of traditional risk factors.

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).

Design: Cohort (spouse pairs) beginning at ARIC visit 1

Exclusions:
Spousal pairs who did not have any follow-up visit after visit 1 or were both diagnosed with diabetes at visit 1 will be excluded. Additionally, if either member of the couple reported being divorced or separated after baseline, the pair will excluded from that time forward. Pairs from a specific visit will only be included in the analyses if both members attended the visit and had information on glucose levels or self-reported physician diagnosis of diabetes.
**Exposure:** The main exposure of interest is being married to a spouse with diabetes.

**Outcome:** Incident diabetes defined based on one of the following: fasting blood glucose level ≥126 mg/dl, non–fasting blood glucose ≥200 mg/dL, hemoglobin A1C ≥ 6.5%, a self-reported physician diagnosis of diabetes, or current use of antidiabetic medication.

**Requested variables (visit 1)**

Demographic variables: age, sex, race, center, educational level (years of education).

Anthropometric measures: weight, BMI and waist circumference.

Health behavioral/lifestyle factors: smoking status (never, current, former) and pack years, physical activity (Baecke PA scores), alcohol use and total daily calorie intake.

Health history and conditions: Parental family history of diabetes, prevalent coronary heart disease, systolic blood pressure, anti-hypertensive medication use and lipid-lowering medication use.

Labs: total and HDL cholesterol, and triglycerides. The following measures will be obtained for visit 1 to 4, whenever available (fasting and non-fasting blood glucose, insulin and hemoglobin A1C).

**Statistical analysis**

Spousal pairs will be defined as previously described (11-14). We will compare baseline diabetes status between husband and wife using McNemar’s test for paired data. Marginal and paired frequencies for diabetes risk factors will be calculated. We will also calculate the Spearman correlation between the husbands’ and wives’ age, caloric intake, systolic blood pressure body mass index and glucose levels at each ARIC visit. We will employ a logistic regression model with generalized estimating equation, assuming unstructured correlation, to calculate the marginal odds ratios for the association of baseline spousal diabetes status with incident diabetes occurring between ARIC visit 1 and December 31, 2012. Sex-specific analyses will be conducted to determine if the effect of the husband’s diabetes status on the wife’s risk is the same as the effect of the wife’s diabetes status on the husband’s risk. Four models with progressive degrees of adjustments for potential confounders will be undertaken. Model 1 will present unadjusted estimates. Model 2 will adjust for age, race, ARIC center and education. Model 3 will further adjust for total caloric intake, systolic blood pressure, smoking status, alcohol intake, body mass index and physical activity (all modeled as time-varying covariates). Model 4 will additionally make adjustment for HDL and total cholesterol. These analyses adjusting for an individual’s risk factors will be repeated incorporating the individuals spouse’s risk factors as well risk factors for both the individual and his/her spouse’s risk factors. Estimates from the unadjusted model will represent the total spousal association including shared norms,
practices, and behaviors. The adjusted models will account for both social and physiological traits (variables that were adjusted) that may be associated with both husband and wife developing diabetes. We will also perform two sensitivity analyses. First, by excluding participants with incident diabetes status defined only by self-report. Second, we will restrict incident diabetes to those occurring after ARIC visit 1 to visit 4. These sensitivity analyses will enable us assess the consistency of the association of spousal diabetes status with incident diabetes across the definitions of diabetes used. For all analyses, a two tailed probability value less than 0.05 will be considered statistically significant. A limitation of our analyses will be the inability to determine the influence of length of marriage or cohabitation, the quality of the marriage or the duration of diabetes ascertained at baseline, on the observed association as such information were not measured. However, some previous studies observed no significant influence of duration of marriage/cohabitation on spousal concordance for diabetes (8).

REFERENCES


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 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 ICTDER 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 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

__✓__ 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)?

Dr. Ellen Demerath has a proposal on spouse correlations in methylation that relates to obesity. However, this proposal is not in the least overlapping.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  ____ Yes  __✓__ 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/
12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript _____ Yes __✓__ No.