ARIC Manuscript Proposal #2042

PC Reviewed: 12/11/12      Status: A      Priority: 2
SC Reviewed: _________      Status: _____      Priority: _____

1.a. Full Title: Sex Differences in the Association of Diabetes with Mortality: A Pooled Cohort Analysis

b. Abbreviated Title (Length 26 characters): Sex, diabetes, and mortality

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

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3. Timeline:
   Analyses will begin following approval of the manuscript proposal by each study’s P&P committee. Preliminary data will be submitted as abstracts to the American Diabetes
Association Scientific Sessions (due January 2013) or the European Association for the Study of Diabetes (due April 2013). A final draft of the manuscript is projected to be ready for submission to each study’s P&P in July 2013.

4. **Rationale:**
Diabetes affects 13% of adults in the US\(^1\) and is associated with an increased risk of mortality.\(^2,5\) However, inconsistent findings have been reported about whether the association between diabetes and mortality varies by sex. Previous studies have reported that diabetes confers an increased risk of mortality for both women and men, with a stronger association reported among women than men.\(^6,7\) Several meta-analyses have reported that women have a higher risk of fatal coronary heart disease (CHD) compared with men with diabetes.\(^8,9\) In contrast, other meta-analyses have reported no statistically significant sex differences in the association of diabetes and CHD mortality.\(^10\) While the previous studies adjusted for cardiovascular risk factors, the inconsistent findings may be due to factors such as differences in cardiovascular risk factors included and the lack of information on diabetes duration. In the Framingham Heart Study, longer diabetes duration was associated with an increased risk of mortality,\(^11\) but prior studies evaluating the diabetes and mortality association have not adequately accounted for diabetes duration. In the Multiple Risk Factor Intervention Trial (MRFIT), an independent association was reported between participants who developed incident diabetes during the study and mortality. However, this study did not include women. The primary objective of this study is to investigate the association of diabetes and mortality, using incident diabetes and not prevalent diabetes, and evaluate whether associations with all-cause and cardiovascular mortality vary by sex. Data from 5 epidemiologic cohort studies will be included in this pooled analysis to evaluate potential sex differences in the diabetes and mortality association.

5. **Main Hypothesis/Study Questions:**
   1. To determine the risk of all-cause and cardiovascular mortality among individuals with incident diabetes compared with individuals without diabetes
      a. To determine whether this association persists after adjustment for demographic and cardiovascular risk factors
   2. To determine whether sex modifies the association of diabetes with all-cause and cardiovascular mortality
      a. To determine whether these differences persist after adjustment for demographic and cardiovascular 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).**
This study will combine data from 5 cohorts (the Atherosclerosis Risk in Communities Study, the Coronary Artery Risk Development in Young Adults Study, the
Cardiovascular Health Study, the Framingham Offspring Study, and the Multi-Ethnic Study of Atherosclerosis) to evaluate sex differences in the association of incident diabetes with mortality. Participants with prevalent diabetes at each study’s baseline examination will be excluded from this analysis.

The primary exposure will be incident diabetes. Incident diabetes will be identified at each study’s follow-up exam based on fasting glucose ≥126 mg/dL or oral hypoglycemic/insulin use measures that are available across all studies. The outcomes will be all-cause mortality and cardiovascular mortality (i.e., myocardial infarction, stroke). Time-dependent Cox proportional hazards models will be used to assess the association between diabetes and mortality and whether this association varies by sex. Diabetes will be defined as a time-varying exposure, such that participants who do not have diabetes at an examination will be classified as unexposed while participants who develop diabetes will be classified as exposed beginning at the examination when they presented with diabetes and for any subsequent examinations. The baseline examination will be the start date for follow-up and the end date will be determined by mortality date or the end of cohort surveillance date. To assess the effects of confounding on the diabetes and mortality association, models will adjust for demographic and cardiovascular factors. Model 1 will be unadjusted. Model 2 will adjust for demographic characteristics (age, race, and education). Model 3 will adjust for the variables in model 2 plus time-varying cardiovascular risk factors (BMI, smoking, hypertension, dyslipidemia, prior CHD, diabetes duration). Model 4 will adjust for the variables in model 2 plus baseline cardiovascular risk factors (BMI, smoking, hypertension, dyslipidemia, prior CHD). Models will be run overall and stratified by sex. Interaction between incident diabetes and sex will be tested to assess potential differences in the diabetes-mortality association by sex. Because data will be pooled from 5 cohorts, additional analyses will also evaluate results using the following: 1) the addition of a covariate to indicate cohort study for the calculation of an overall hazard ratio and 2) the calculation of separate hazard ratios within each cohort study that will be pooled together using fixed or random effects. Secondary analyses will explore possible interactions by race and age and alternative definitions of diabetes using measures (e.g., HbA1c ≥ 6.5% or OGTT >200 mg/dL) that are not available in all studies.

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 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  _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.cscu.unc.edu/ARIC/search.php  
_____ Yes   ___X___ 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.cscucc.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.cscucc.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.
References


