ARIC Manuscript Proposal #3033

PC Reviewed: 8/8/17  Status: _____  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

1.a. Full Title: Short-term mortality and cardiovascular risk in older adults with diabetes or prediabetes

b. Abbreviated Title (Length 26 characters): Diabetes and short-term CVD and death

2. Writing Group:
   Writing group members: Elizabeth Selvin; Dan Wang; John W. McEvoy; A. Richey Sharrett; Josef Coresh; Gwen Windham

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
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3. Timeline: Data are currently available. We aim to complete the manuscript <1 year from the time of approval.

4. Rationale:
Older adults are at increased vulnerability for diabetes but there is heterogeneity in the presentation and severity of the disease in older populations (1-3). There is limited evidence for screening and appropriate glycemic targets, and how best to reduce cardiovascular risk and mortality in this population. Among adults older than 75, the evidence gap is particularly evident. There is also controversy regarding prognosis in older persons with hyperglycemia below the threshold for a diagnosis of diabetes.

The objective of this study is to characterize the short-term (~3 year) risk of cardiovascular disease and mortality in older adults with prediabetes, undiagnosed diabetes, and diagnosed diabetes. We will evaluate the prognostic performance of current diabetes and prediabetes diagnostic criteria in older adults. In adults with a prior diagnosis of diabetes, we will examine potential differences in risk according to various diagnostic criteria and examine potential differences by diabetes duration and diabetes medication use. We will also specifically examine differences by age, sex, and race.

5. **Main Hypothesis/Study Questions:**

**Study Aim:** To compare short-term cardiovascular and mortality risk (absolute and relative risk) in persons with prediabetes and diabetes to those persons without diabetes at ARIC visit 5. We will also compare clinical cut-points for prediabetes and diabetes based on fasting glucose and HbA1c. In persons with diagnosed diabetes, we will examine differences in risk by duration of diabetes and diabetes medication use. We will formally test for interactions in associations by age, sex, and race.

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).**

**Study design:** Prospective cohort analysis of participants from the Atherosclerosis Risk in Communities (ARIC) Study who attended the visit 5 examination from 2011 to 2013, which will serve as baseline for the present study (mean age 76, range 66 to 90).

**Inclusion/exclusions:** We will exclude those participants missing information on diabetes status, HbA1c, glucose, those who fasted <8 hours (5.2% of visit 5 participants), and those who are missing relevant covariates of interest at visit 5.

**Exposures:** Diabetes status defined as normoglycemic, prediabetes, undiagnosed diabetes, or diagnosed diabetes based on information available at or before visit 5. Persons who self-report a physician diagnosis of diabetes or who are currently taking glucose-lowering medications will be classified as having diagnosed diabetes. In persons without a prior diagnosis of diabetes, we will compare American Diabetes Associations definitions for undiagnosed diabetes and prediabetes based on fasting glucose (<100, 100-125, >=126 mg/dL) and HbA1c (<5.7, 5.7-6.4, >=6.5%).

**Outcomes:** All-cause mortality and cardiovascular events (coronary heart disease, stroke, or heart failure) occurring after visit 5. ARIC participants are contacted annually by telephone (semi-annually after 2012) and reported hospitalizations and deaths are identified. ARIC investigators also survey lists of discharges from local hospitals and death certificates from state
vital statistics offices for potential events. Hospital records are abstracted and potential coronary heart disease, ischemic stroke, and heart failure events are adjudicated by an end points committee. There is currently a median of ~2.6 years of post-visit 5 follow-up for mortality (maximum of 3.6 years) and median of ~2.6 years of follow-up for cardiovascular events (maximum of 3.6 years).

**Coronary heart disease:** We will define incident coronary heart disease cases using the composite adjudicated definition incorporating definite or probable myocardial infarction, cardiac procedures, and deaths from coronary heart disease identified during active surveillance for all hospitalizations and deaths among ARIC participants.

**Ischemic stroke:** We will define incident stroke as an adjudicated (definite or probable) incident ischemic stroke event identified during active surveillance.

**Heart failure:** We will define incident heart failure as an adjudicated heart failure event identified during active surveillance.

**Mortality:** Death from any cause identified during active surveillance.

**Covariates:** age, sex, race-center, prevalent cardiovascular disease, total cholesterol, LDL-cholesterol, treatment for high cholesterol, triglycerides, HDL-cholesterol, systolic blood pressure, diastolic blood pressure, hypertension medication use, education levels, family history of diabetes.

**Statistical analyses:**
We will compare baseline characteristics by diagnosed diabetes status and using definitions based on fasting glucose and HbA1c We will conduct survival analysis using Kaplan-Meier to examine the cumulative incidence of cardiovascular disease and mortality by diabetes status. We will calculate incidence rates (per 1,000 person years). We use Cox proportional hazards models to generate hazard ratios and corresponding 95% confidence intervals to characterize the association of diabetes status with cardiovascular risk and mortality with adjustment for relevant covariates. We will evaluate the proportional hazards assumption using log(-log) plots and by testing risk factor-by-time interactions; if the assumption is violated the interactions term(s) will be kept in the model and the time-dependent nature of the risk will be interpreted accordingly.

We will compare models with adjustment for the variables listed below:

Model 1: age, sex, race-center
Model 2: age, sex, race-center, prevalent cardiovascular disease, total cholesterol, LDL-cholesterol, treatment for high cholesterol, triglycerides, HDL-cholesterol, systolic blood pressure, diastolic blood pressure, hypertension medication use, education levels, family history of diabetes.

Additional model in persons with diagnosed diabetes only:
Model 3: all variables in Model 2 + HbA1c, diabetes medication type
We will test for interactions by age (<75, >=75 years), sex, and race using the likelihood ratio test.

Limitations:
- As with all observational studies, we will not be able to eliminate the possibility of residual confounding.
- Because there is currently a maximum of 3.6 years of follow-up of ARIC participants after visit 5, we will only be able to examine short-term cardiovascular risk and mortality. However, if updated data files become available, we will update our analyses with the most recent data available prior to submission for ARIC review.
- Reliance on single measures of HbA1c and glucose to characterize prediabetes and diabetes whereas clinical practice recommendations are to repeat tests to confirm elevations in either fasting glucose or HbA1c.

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

   ____X____ Yes  ____ No

ARIC Manuscript Proposal #2485 - Risk prediction of microvascular and macrovascular complications and all-cause mortality in persons with diabetes  Christina M. Parrinello

ARIC Manuscript Proposal #2129 - Diabetes and prediabetes and the incidence and progression of subclinical myocardial injury  Elizabeth Selvin

ARIC Manuscript Proposal #2649- Comparative Prognostic Performance of Different Definitions of Prediabetes  Bethany Warren
ARIC Manuscript Proposal # 1024 - Glycemic Control (HbA1c) and Coronary Heart Disease Risk in Persons with and Without Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study Selvin, E.

ARIC Manuscript Proposal #592 - Disease progression and mortality in older americans (MS592) Kim, Y.

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* _2009.16_______)
   ____ 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, approved manuscripts using 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 __X__ No.

References