

ARIC Manuscript Proposal #1911

PC Reviewed: 5/8/12
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Incident Type 2 Diabetes among Younger and Middle-Aged African American and White Adults: ARIC, CARDIA, and the Framingham Heart Study

b. Abbreviated Title (Length 26 characters): Incident diabetes in younger vs. middle-age

2. Writing Group:

Writing group members: Gina Wei; Sean Coady; Jared Reis; David Goff, Jr.; Mercedes Carnethon; Frederick Brancati; Elizabeth Selvin; Joseph Coresh; David Jacobs; Ralph D'Agostino, Sr.; Caroline Fox

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

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3. Timeline: Analysis will be done over the next few months with the goal of submitting an abstract either to the AHA Scientific Sessions (November 2012) or AHA Epi Council Meeting (Spring 2013) and submitting the paper to a journal shortly thereafter.

4. Rationale: Prior research on incidence and clinical predictors of type 2 diabetes has largely been focused on the middle-aged population (1,2). Some well-recognized clinical predictors in this group include obesity, hypertension, low HDL levels, elevated triglyceride levels, impaired fasting glucose, and parental diabetes (2). In comparison, research on incident type 2 diabetes and its clinical predictors in younger adults is relatively limited and often restricted by its design – either cross-sectional (3), restricted to a single ethnic group (4), or relied on self-reported data (4,5). To our knowledge, no study has directly compared the incidence or clinical predictors of diabetes between younger vs. middle-aged populations. It is still unclear whether the clinical factors identified in the middle aged similarly predict incident type 2 diabetes in those approaching middle age; and if so, to what extent the predictors’ relative impact differs between these groups. Furthermore, the association between the burden of being overweight or obese during follow-up (i.e., BMI years above overweight/obesity defined as the area above the overweight or obesity threshold during the follow-up period) and the risk of developing type 2 diabetes, after adjustment for baseline BMI and other cardiometabolic risk factors, has not been well quantified in either of these age groups, particularly comparing African Americans to whites (5-7).

Together, CARDIA, ARIC, and the Framingham Offspring Study provide a richly combined dataset to compare the incidence and clinical predictors of type 2 diabetes in younger vs. middle-aged adults, and to further determine whether differences exist between African Americans and whites. Carefully measured longitudinal data on major “baseline” clinical predictors, as well as prospective obesity burden and diabetes status, are available for both African Americans and whites. The combined age range represented by the three cohorts also encompasses a sufficiently broad spectrum that is required for such comparisons.

5. Main Hypothesis/Study Questions:

1. To compare the risk of incident diabetes among younger (age >30 and <45 years at baseline) and middle-aged (>45 and <60 years at baseline) African American and White adults.

2a. To determine whether the risk between baseline cardiometabolic risk factors and incident diabetes differs between younger and middle-aged adults.

Hypothesis: Most risk factors, including obesity, will have a greater effect on risk of developing diabetes in the younger group (v. the middle-aged group).

2b. To determine the degree to which BMI years above overweight/obesity during follow-up is associated with increased risk of diabetes, above and beyond baseline BMI and other cardiometabolic risk factors, and to determine whether this association differs between younger and middle-aged adults.

Hypothesis: Greater prospective cumulative burden of obesity will also have a greater effect on risk of developing diabetes in the younger group (v. middle-aged group).

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).

ARIC participant inclusion/exclusion: Inclusion: < 60 years old at the ARIC Cohort Exam 1 (1987-89). Exclusion: free of diabetes at baseline and returned for at least one follow-up exam.

Definitions of Diabetes: Diabetes will be defined similarly across the cohorts in the following way: fasting blood glucose ≥ 126 mg/dL, casual blood glucose ≥ 200 mg/dL, or using insulin or oral hypoglycemic medication. Time-to-diabetes will be estimated using a previously described method by Duncan et al. (13). That is, for cases ascertained based on blood glucose value, the incident date will be estimated by linear interpolation using the glucose values at the ascertaining and previous examinations. For cases ascertained based on the use of diabetic medications, the time-to-diabetes will be estimated by using their fasting glucose at the earlier visit and a slope estimated using information from all diabetic subjects who had been unaware of their status (because the fasting glucose at ascertainment for those who were on diabetic medication may have been affected by their knowledge of their diabetes status).

Analytic Plan: We will conduct pooled analyses using individual participant-level data from CARDIA, ARIC, and Framingham Offspring Study. Furthermore, we will add a meta-analysis approach that pools study-level summary data and compare it with our main results (i.e., one that pools individual participant-level data). Diabetes incidence will be described using person-years of observation. Baseline characteristics of those developing diabetes will be compared to those not developing diabetes using race specific, standard linear models after adjustment for age and sex. Cox proportional hazards models will be used for the principal multivariate analysis. The association of prospective BMI with incident diabetes will utilize baseline covariates along with a 'BMI-years-above overweight or obesity', time-dependent covariate. In brief, the time dependent covariate will be calculated as the area above the BMI based overweight or obesity threshold (≥ 25 , ≥ 30) at each event point for participants at risk for incident diabetes. Two approaches will be used to study how the association of the baseline covariates and the time-dependent covariate may differ in younger versus middle-aged participants. In the **first approach**, an age cohort indicator variable will be used to classify participants into the two age groups (younger: 30-44 years of age at baseline, middle-aged: 45-59 years of age at baseline; note that the age span of both groups will be similar at 15 years). Interaction terms between the indicator variable and the covariates will be used to test for differences in associations by baseline age. In the **second approach**, time dependent interaction terms will be used to test the association of risk factors with incident diabetes before age 45 with incident diabetes on or after age 45. In both approaches, models will be race specific and time will be measured using age (entry age and exit age). An overall model will be used to examine potential race differences.

References

1. Brancati FL, Kao WH, Folsom AR, Watson RL, Szklo M: Incident type 2 diabetes mellitus in African American and white adults: the Atherosclerosis Risk in Communities Study. *JAMA* 283:2253-2259, 2000
2. Wilson PWF, Meigs JB, Sullivan L, Fox CS, Nathan DM, D'Agostino RB, Sr.: Prediction of Incident Diabetes Mellitus in Middle-aged Adults: The Framingham Offspring Study. *Arch Intern Med* 167:1068-1074, 2007
3. Hillier TA, Pedula KL: Characteristics of an adult population with newly diagnosed type 2 diabetes: the relation of obesity and age of onset. *Diabetes Care* 24:1522-1527, 2001
4. Brancati FL, Wang NY, Mead LA, Liang KY, Klag MJ: Body weight patterns from 20 to 49 years of age and subsequent risk for diabetes mellitus: the Johns Hopkins Precursors Study. *Arch Intern Med* 159:957-963, 1999
5. Lee JM, Gebremariam A, Vijan S, Gurney JG: Excess Body Mass Index-Years, a Measure of Degree and Duration of Excess Weight, and Risk for Incident Diabetes. *Arch Pediatr Adolesc Medarchpediatrics*, 2011
6. Schienkiewitz A, Schulze MB, Hoffmann K, Kroke A, Boeing H: Body mass index history and risk of type 2 diabetes: results from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *The American Journal of Clinical Nutrition* 84:427-433, 2006
7. Everhart JE, Pettitt DJ, Bennett PH, Knowler WC: Duration of obesity increases the incidence of NIDDM. *Diabetes* 41:235-240, 1992

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 ICTDER03 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.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)?

- Heterogeneity in the relationship between race, adiposity, insulin, and incident diabetes (Mercedes Carnethon)
- Demographic, Behavioral and Clinical Factors associated with the Incidence of Normal Weight Type 2 Diabetes (Mercedes Carnethon)

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.csc.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.csc.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.