ARIC Manuscript Proposal # 1762

PC Reviewed: 3/8/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Epidemiologic Studies of Type 2 Diabetes in Normal Weight Adults: Cardiovascular and All-Cause Mortality

b. Abbreviated Title (Length 26 characters):
Normal weight diabetes mortality

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

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3. Timeline:

Analyses are ongoing as the data were released under the approved ancillary study, "Epidemiologic Studies of Type 2 Diabetes in Normal Weight Adults". We will prepare the manuscript for submission to a journal in May 2011.

4. Rationale:

T2DM in normal weight persons is an intriguing and understudied representation of the MONW phenotype that has become increasingly common over time.[1] Cardiovascular diseases, including CHD and stroke, are the leading cause of death for persons with T2DM. However, little is known about the micro- and macro-vascular consequences of T2DM in the absence of obesity. The question is particularly important because of the presence of uncontrolled confounding by obesity, which may be associated with cardiovascular mortality through independent pathways. Existing studies cannot answer these questions because of the small numbers of normal weight persons with T2DM in any single study.

We propose to pool data from the Atherosclerosis Risk in Communities (ARIC), Cardiovascular Health Study (CHS), Coronary Artery Risk Development in Young Adults (CARDIA), Framingham Offspring Study (FOS), and Multi-Ethnic Study of Atherosclerosis (MESA) to compare the rates of cardiovascular complications between normal weight and overweight/ obese persons who experienced incident T2DM. The resulting pooled dataset will include a large, diverse (e.g., race/ethnic, gender, and age) sample of participants with incident T2DM and the largest sample to date of participants who were normal weight when T2DM was identified.

Our proposed analysis provides a unique opportunity to investigate an uncommon, but scientifically important, representation of the metabolically obese normal weight individual—the normal weight person with T2MD. Given the increasing numbers of such persons in our society, due in part to aging of the population and increasing race/ethnic diversity, findings from the present study are likely to be of use to a larger segment of society than ever before. The strength of our pooled secondary data analysis approach is that we will have adequate statistical power to identify multiple characteristics associated with the development of T2DM in normal weight persons as compared with overweight persons with T2DM.

5. Main Hypothesis/Study Questions:

Our objective is to use longitudinal follow-up data from each of the cohorts to compare the all cause and cardiovascular (secondary) mortality rates in participants who were normal vs. overweight/obese persons at incident T2DM. We hypothesize that total and cardiovascular mortality rates will be higher among overweight/obese persons with T2DM as compared with normal weight persons who develop T2DM.

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).

Inclusions/exclusions

Cohort participants with incident T2DM and who are free from clinical CVD at baseline comprise the analytic sample for this Aim. All study participants who were free from T2DM and prevalent cardiovascular disease (CVD) at their baseline examination will be studied in this aim. Because our goal is to investigate the incidence of CVD morbidity and mortality after

T2DM, participants who experience clinical CVD prior to the identification of T2DM will be excluded from this analysis. Although Jackson Heart Study (JHS) is included in testing for the other aims of this project, cohort surveillance beyond the last clinical examination was not available and so they are not included in our analyses to test this aim.

Variables

In brief, we will include the following sociodemographic characteristics from baseline and each follow-up examination of CHS and other studies: age, sex, race/ethnicity, and education. Cardiovascular disease risk factors included as covariates are: systolic and diastolic blood pressure, antihypertensive medication use, total cholesterol and HDL cholesterol, smoking status and physical activity.

Prevalent CHD at baseline will be defined as a validated self-report of physician-diagnosed MI, history of coronary artery bypass grafting (CABG), coronary angioplasty, use of nitroglycerin at baseline, or evidence of previous MI based on the presence of major Q waves or the combination of minor Q waves and ST-T wave changes.

All-cause and cardiovascular mortality. Mortality is determined using ARIC surveillance files up through 2006. Cardiovascular mortality is defined as all atherosclerotic CHD (fatal MI and definite and possible fatal CHD), cerebrovacular disease (fatal ischemic and hemmorhagic stroke) and other atherosclerotic and cardiovascular deaths.

Type 2 Diabetes (T2DM) will be defined according to the American Diabetes Association (ADA) 2003 fasting glucose criterion ($\geq$126 mg/dL) or report of oral hypoglycemic mediation or insulin. We chose each of the studies because fasting glucose was available at baseline and at least one follow-up examination. We will not use 2-hour oral glucose tolerance test (available at examination 4 in ARIC) because not all of the studies have this particular measure. Preliminry analyses indicate that 1357 participants in ARIC have incident diabetes (9% are normal weight); across cohorts there are 2,764 participants who incident diabetes and the prevalence of incident diabetes who are normal weight ranges from 9 to 21%.

Weight status. Body weight (kg) and height (m) will be abstracted from each clinical examination. Participants will be categorized as normal weight (BMI<25 kg/m^2) or overweight/obese (BMI $\geq$25 kg/m^2) at the time T2DM is initially identified. We will carry out secondary analyses excluded participants who are underweight (BMI<18.5 kg/m^2).

Brief analysis plan and methods:

We will carry out our analyses separately within cohorts and use meta-analytic strategies to combine data and we will carry out our analyses using a pooled cohort with common variables. Variabels that are not measured using similar scales across cohorts (e.g., physical activity) will be standardized to create z scores).

We will use Cox proportional hazards modeling to compare and test the time-to-incident morbid events or mortality between normal weight and overweight/obese (referent group)

persons with T2DM. Follow-up time will be calculated as the difference in the time from initial identification of incident T2DM to mortality or the end of follow-up, whichever comes first. Prior to modeling, we will test and confirm the proportional hazards assumption using log-log survival plots. After computing unadjusted Kaplan-Meier curves, we will employ multivariable modeling to adjust for baseline demographic characteristics (e.g., age, sex, race) and other metabolic risk factors (e.g., blood pressure, smoking status, physical inactivity, antihypertensive medication use, and lipids). We will carry out secondary analyses excluding participants who were underweight (BMI<18.5) and those whose follow-up time is shorter than 2 years to reduce the probability that weight loss immediately prior to death is driving any observed associations.

References

1. Ruderman NB, Schneider SH, Berchtold P. The "metabolically-obese," normal-weight individual. *Am J Clin Nutr.* 1981;34(8):1617-1621.
2. St-Onge MP, Janssen I, Heymsfield SB. Metabolic syndrome in normal-weight Americans: new definition of the metabolically obese, normal-weight individual. *Diabetes Care.* 2004;27(9):2222-2228.
3. Ruderman N, Chisholm D, Pi-Sunyer X, Schneider S. The metabolically obese, normal-weight individual revisited. *Diabetes.* 1998;47(5):699-713.
4. Willerson JT, Ridker PM. Inflammation as a Cardiovascular Risk Factor. *Circulation.* 2004;109(21_suppl_1):II-2-10.

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 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 _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.cscc.unc.edu/ARIC/search.php

_X__ 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)?

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.cscc.unc.edu/aric/forms/

12. 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.