ARIC Manuscript Proposal #3319

PC Reviewed: 1/8/19 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:
Overweight and adiposity in young adulthood and the risk of incident diabetes: a pooled cohorts study
Parent study:
Potential future benefits of cardiovascular risk factor control in today's young adults (R01HL107475-04)

b. Abbreviated Title (Length 26 characters): Young adult BMI and diabetes

2. Writing Group:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. NN

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3. Timeline: The analyses will be completed within six months, and the full manuscript within one year, following approval of this manuscript proposal.

4. Rationale:
It has been estimated that more than 30.3 million people in the US (9.4% of the US population) had diabetes in 2015, with another 84.1 million adults (33.9% of the population) having pre-diabetes.[1] Type 2 diabetes accounts for 90 to 95% of these cases of diabetes in the population as a whole. The impact of this high prevalence of disease, both on the health of individuals and on the costs to patients and society, is remarkable. In 2014, 7.2 million adult hospital discharges included a listed diagnosis of diabetes, along with 14.2 million emergency medicine visits, including 245,000 visits for

hypoglycemia and 207,000 visits for hyperglycemic crisis.[2] In 2012, diabetes was the 7th leading cause of death and the estimated direct and indirect costs of this disease in the US were $245 billion.[3] Age and sex-adjusted estimates of medical expenditures are 2.3 times higher in patients with diabetes than in those without.[3]

Diabetes has been identified as a risk factor for multiple adverse health outcomes including cardiovascular disease, kidney disease, and retinopathy. Patients with "pre-diabetes" are also at increased risk for heart disease and stroke, as well as progression to diabetes. Multiple studies have sought to determine the risks associated with development of diabetes. Overweight and obese status have been established as risk factors for development of diabetes as demonstrated in multiple large-scale studies.[4] A variety of measures of obesity including body mass index (BMI) and waist circumference (WC), have been found to predict obesity-related health risks including diabetes. Some evidence suggests that waist circumference alone is a stronger predictor of obesity-related risks than BMI alone,[5] although one meta-analysis found that BMI, WC, waist-hip ratio, and waist-height ratio all had similar predictive values for incident diabetes.[6] In addition to increasing risks for development of diabetes, overweight and obese status often leads to adverse cardiometabolic risk profiles including high blood pressure and hyperlipidemia.[7] Some of these risk factors have independently been identified as risk factors for diabetes, suggesting that they may partly mediate the association between overweight/obesity and diabetes. An analysis of participants from the Framingham Offspring Study found that metabolic syndrome traits (including hypertension, low LDL, elevated triglycerides, and impaired fasting glucose) predicted the risk of incident diabetes independent of obesity status.[8] Additionally, the association between obesity and diabetes may differ by race/ethnicity, with African-American individuals having an increased risk of developing diabetes compared to whites at the same level of BMI.[9]

Although overweight and obesity have been shown to be important risk factors for incident diabetes, most studies have examined this association in middle-aged and older adults. Attempts have been made to capture the impact of young adulthood weight status on later life incident diabetes via self-report of younger adult weights, [10] but it is largely unknown if young adult exposures to elevated BMI or WC (between ages 18 and 39 years) are associated with the development of diabetes later in life (after age 40), independent of later life BMI/WC. Furthermore, compared to BMI measured at a single time point, studies have shown that cumulative exposure to BMI is a better predictor of incident diabetes.[11] When thinking about screening programs in adults, an understanding of the risk of young adulthood overweight and obesity on diabetes incidence could have important clinical implications, as by the time of a clinical diabetes diagnosis a patient may have been exposed to years of vascular and other end-organ damage related to hyperglycemia and other sequelae of incipient diabetes. Young adulthood may be a critical period for identifying diabetes risk factors and intervening to prevent or delay later life diabetes using lifestyle measures. Nonetheless, current guidelines recommend reserving diabetes screening for middle-aged adults, and as a result, health care providers may defer assessment of diabetes risk when patients are younger. For example, the US Preventive Services Task Force guideline recommends screening asymptomatic patients starting at age 40 years only if they are overweight or obese, come from a high-risk ancestry group, or have an additional risk characteristic.[12] The American Diabetes Association (ADA), on the other hand, recommends screening all adults, including young adults (starting at age 18 years) who are diagnosed as overweight or obese and who have least one additional risk factor, as well as all asymptomatic adults (regardless of BMI or other factors) starting at age 45 years.[13] Our study aims to examine the independent contribution of exposures to elevated BMI and/or WC during young adulthood (age 18 to 39 years) to the development of incident diabetes and pre-diabetes, controlling for later life BMI and WC exposures (age $\geq$ 40 years). Findings from this study may help re-define the optimal age for initiating diabetes screening, risk assessment, and primary prevention strategies in the U.S. population.

5. Main Hypothesis/Study Questions:

Aim 1: To examine the association between cumulative exposures to elevated BMI and larger WC during young adulthood (age 18 to 39 years) and the risk of incident diabetes and pre-diabetes later in life, controlling for later life BMI and WC (age $\geq$ 40 years).

We hypothesize that exposures to elevated BMI and larger WC in young adults are associated with the development of incident diabetes and pre-diabetes later in life, independent of later life exposures.

Aim 2: To examine if the association between young adult BMI and WC with incident diabetes and pre-diabetes are mediated by young adult exposures to other cardiometabolic risk factors (systolic blood pressure [SBP], diastolic blood pressure [DBP], low-density lipoproteins [LDL], high-density lipoproteins [HDL], triglycerides [TG], homeostatic model assessment of insulin resistance [HOMA-IR]).

We hypothesize that the associations between young adult BMI and WC with later life incident diabetes and pre-diabetes are partially mediated by young adult exposures elevated SBP, LDL, triglycerides, HOMA-IR, and low HDL.

Aim 3: To examine if sex or African American race/ethnicity modify the associations between young adult BMI and WC with later life incident diabetes and pre-diabetes.

We hypothesize that the association between young adult BMI and WC with later life diabetes outcomes will be stronger in African Americans compared with non-African Americans, but the association will not be modified by sex. Though data are limited in our Pooled Cohorts for Hispanic Americans and Asian Americans, we will test for effect modification for these groups in exploratory analyses.

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).

We have previously harmonized and pooled individual-level basic cardiovascular disease risk factor and outcomes data from the main ARIC study with similar data from several other NIH-funded prospective cohort studies (ARIC ancillary study 2016.18; related ancillary study proposals approved for ARIC, CARDIA, CHS, MESA, Framingham Offspring, and Health ABC). The pooled data permit us to model risk across the adult years, and provide a sufficient number of incident diabetes events to support robust inferences that may be generalizable to the entire adult U.S. population. Inclusion of ARIC will be an essential component of this work given its robust data in young adults, racial/ethnic diversity, meticulous follow-up, and gold-standard measures of cardiometabolic risk factors.

Outcome definition:
Primary outcome: Incident diabetes will be identified by self-report of diabetes, fasting glucose levels ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, or use of diabetes medications.

Secondary outcomes:
1) Diabetes (alternative definition): defined as self-report of diabetes, fasting glucose levels ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, HbA1c ≥ 6.5%, or use of diabetes medications.
2) Pre-diabetes: defined as fasting glucose 100-125 mg/dL AND no diabetes medication use.
3) Pre-diabetes (alternative definition): defined as fasting glucose 100-125, HbA1c 5.7–6.4% AND no diabetes medication use.

Variables to be Used:
Demographic variables: Age, sex, race/ethnicity, education, family income, study sites
Anthropometric variables: Height, weight, BMI, WC
Lipid variables: Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, use of lipid-lowering medication
Blood pressure variables: SBP, DBP, use of antihypertensive medication
Other clinical variables: Smoking status, age of smoking initiation, age of smoking cessation, cigarettes per day, alcohol drinks per day, serum creatinine, urine creatinine, urine albumin, history of CVD
Diabetes variables: Fasting status, serum glucose, insulin, HbA1c, use of diabetes medications, self-reported history of diabetes, history of gestational diabetes, family history of diabetes, 2-hour oral glucose tolerance test

Statistical analyses. As in our prior analyses of the association between young adult risk factor exposures and CVD outcomes,[14-16] we will impute lifetime risk factor trajectories for BMI, WC, fasting glucose, fasting insulin, SBP, DBP, triglycerides, LDL, HDL starting from age 18 for every participant. To accomplish this, we will use linear mixed models to estimate latent trajectories underlying the observed values for each participant, and imputed risk factor levels annually from age 18 years until the end of follow-up for each participant. Individual trajectories will then be used to estimate time-weighted average (TWA) exposures (similar to "pack years" of tobacco exposure) to each risk factor during young adulthood (age 18-39 years) and later adulthood (age ≥40 years). Age of diabetes onset and age of medication initiation will be imputed by randomly drawn from a conditional distribution estimated using log-normal survival models.[16,17]

Cox proportional hazards model will be used to estimate the associations between young adult BMI and WC with the risks of incident diabetes and pre-diabetes. We will use age as the time scale, with the origin for time to event set at 40 years. Models will be adjusted for race/ethnicity, sex, birth year, family income, education level, smoking status, and later adult TWAs of BMI and WC. To examine whether the associations between young adult BMI and WC with diabetes outcomes are mediated by young adult exposures to other cardiometabolic risk factors (SBP, DBP, LDL, HDL, triglycerides, HOMA-IR), we will assess the change in the β-coefficient of BMI and WC comparing the base model (without adjustment for other cardiometabolic factors) and the model further adjusted for young adult TWAs of other cardiometabolic risk factors. The 95% CIs for the difference in the β coefficients between the 2 models will be calculated using bootstrap methods with 1000 replications. To examine potential interactions by race/ethnicity and sex, we will include interaction terms of young adult BMI (or WC) by race/ethnicity and by sex in the Cox models. Additionally, to examine the robustness and consistency of our findings, we will perform several sensitivity analyses, including additionally adjusting for the most recent directly observed value carried forward; excluding individuals who ever used anti-hypertensive or lipid lowering medications; repeating analyses by cohort, as well as leaving out one cohort at a time to confirm that our findings were not driven by any single study. All analyses were performed using STATA version 14.[17]

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? __n/a__ Yes __n/a__ 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.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html

___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)?

No prior ARIC manuscript proposals have looked at the association between young adult exposures to BMI and WC with the risk of incident diabetes and pre-diabetes later in life. The other proposals related to overweight/obesity and incident diabetes:

#2471: Weight change and incident diabetes: the Atherosclerosis Risk in Communities Study
#3030: Adulthood weight history, incident diabetes, and death

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes _x___ 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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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.

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