ARIC Manuscript Proposal #3030

1.a. Full Title: Adulthood weight history, incident diabetes, and death

b. Abbreviated Title (Length 26 characters):

2. Writing Group: Molly Jung, Casey M. Rebholz, June Stevens, Josef Coresh, Chiadi Ndumele, and Elizabeth Selvin. Others are welcome.

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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3. Timeline:

- We plan to complete a draft of the manuscript within one year of the proposal approval.
4. **Rationale**:

The prevalence of overweight and obesity have increased dramatically over the past three decades in the U.S.; currently, two out of three adults are overweight (body mass index [BMI], 25-<30 kg/m²) or obese (BMI >30 kg/m²) (1). Overweight and obesity disproportionately affect racial/ethnic minority groups and contribute to health disparities in the U.S. (2,3). Most prior epidemiologic studies on overweight or obesity and health outcomes have assessed BMI at one time-point (4–6). A single measure of BMI may be problematic as a means to fully characterize the association of adiposity with health outcomes because it does not account for prior weight history. That is, individuals with normal BMI (BMI, 18.5-<25 kg/m²) may include a mix of persons who were never overweight or obese plus persons who recently lost weight (typically, significant weight loss is unintentional). Likewise, the overweight or obese categories may include persons who have steadily gained small amounts of weight over a long period of time and persons who gained a significant amount of weight over a short period of time.

For obesity-related diseases, BMI history may be more informative than a single measure of BMI because the effects of obesity are believed to compound over time and increase with greater severity (7,8). For example, persons who were moderately obese for a long duration may have similar diabetes risk compared to others who are severely obese for a short duration. In the US, longitudinal studies have shown that large weight gain typically occurs in early adulthood and is maintained or modestly increases in midlife (9). Additionally, weight loss is more likely attributed to a cachexia-causing disease because healthy long-term weight loss is uncommon (10,11). For mortality, accounting for weight history has helped explain the “obesity paradox” which are the counterintuitive findings where normal weight persons have worse prognosis than moderately overweight persons (12,13). In some analyses that have excluded individuals with cachexia-causing diseases, higher BMI has been found to indeed be associated with increased mortality (14–16).

Using data from the Atherosclerosis Risk in Communities (ARIC) Study, we aim to evaluate if past BMI trajectories in midlife (visits 1 through 4) add prognostic information above and beyond a single measure of BMI (visit 4) for diabetes risk and mortality. Accounting for weight histories when considering diabetes and mortality may have different implications because obesity is a major specific risk factor for diabetes, and is less specifically associated with mortality. We will also evaluate if BMI change from early adulthood (self-reported weight at age 25) to mid-life (visit-based measures of BMI) contributes information to diabetes risk beyond midlife BMI. We will address the study questions in the overall study population and by sex and race.

The ARIC study is particularly well suited to examine the association of weight trajectories with health outcomes. Weight history was assessed both in early adulthood (age 25 by self-report) and midlife (measured at visits 1, 2, 3, and 4). The follow-up time for incident diabetes and mortality after exposure assessment (visit 4) is over 15 years.
5. **Main Hypothesis/Study Questions:**

Aim 1: To evaluate whether BMI trajectories in midlife (visit 1 through 4) add prognostic information above and beyond a single measurement of BMI in midlife (visit 4) for diabetes risk and mortality after visit 4 (maximum of 17 years of follow-up).

Hypothesis 1: We hypothesize that change in BMI in midlife will add significant prognostic information to baseline midlife BMI for diabetes risk. Additionally, weight loss in midlife is more likely due to a cachexia-causing disease rather than healthy weight loss methods; therefore, we hypothesize that weight change will be associated with mortality above and beyond a single measure of BMI.

Aim 2: We will also evaluate if BMI change from early adulthood (self-reported weight at age 25) to midlife (visit-based measures of BMI) contributes information to risk beyond midlife BMI (visit 4).

Hypothesis 2: Change in BMI from early adulthood to midlife will add significant prognostic information beyond midlife BMI for both diabetes risk and mortality.

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).**

Inclusion/exclusion: We will include all participants without prevalent diabetes at the baseline exam (visit 4, 1996-1998). Due to small numbers, we will exclude the following participants: 1) those who do not self-identify as either white or black; 2) blacks from the Washington County, Maryland field center; and 3) blacks from the Minneapolis, Minnesota field center. We will also exclude participants missing relevant BMI measurements and participants missing data on incident diabetes. We will also exclude participants who are missing covariates.

**Design:** Prospective cohort analysis. We will summarize measured BMI history between visits 1 and 4 and age 25 (self-report at visit 1) and visit 4. Prospective follow-up for incident diabetes and mortality will begin at visit 4 and is available through December 2014 (to be updated with most current data available as appropriate).
**Exposures:** BMI is calculated as weight in kilograms divided by height in squared meters. Up to five measurements are available for the calculation of BMI: self-reported weight at age 25 (reported at visit 1) and measured height and weight at visits 1 through 4. More specifically, weight was measured at visits 1 (1987-89), 2 (1990-93), 3 (1993-95), and 4 (1996-98). Height was measured at visits 1, 3, and 4. Height from visit 1 will be used to calculate BMI at age 25, and visits 1 and 2.

Percent change in BMI between two time points will be calculated during mid-adulthood (visits 1-4) and during early adulthood (age 25-visit 1). We will consider the following categories of change: >10% loss, 10-5% loss, 5% loss to 5% gain, 5-10% gain, and >10% gain.

To evaluate average BMI change using repeated measurements, we will use linear mixed effects models with random intercepts and slopes for each participant. This model is flexible and will allow for repeated measurements and unequal intervals between participants. We will assess BMI by age and will use higher order terms to allow differing curvatures in the longitudinal changes. We will use the predicted BMI slopes in midlife (visits 1, 2, 3, and 4) as an exposure definition.

Long-term burden of BMI will be assessed using the area under the curve using two methods. In the first method, we will calculate the area under the curve of BMI by age. In the second method, we will calculate area under the curve of BMI by age of growth curves using multiple measurements of BMI (age 25 and visits 1, 2, 3, and 4) by age, as done in Cook et al 2004 (17).

The area under the curve will be calculated from growth curves of BMI by age using linear mixed models with random intercepts and slopes. Age and its higher order terms (i.e., age², age³, etc.) will be included in the model to account for differences in the curvature of the longitudinal BMI measurements. Higher order age terms will be excluded if it is not statistically significant at $P<0.05$, if the inclusion makes a lower ordered term not statistically significant, or if the model does not converge. We will center age at the median value to reduce collinearity with higher order terms. We will also consider dividing the higher order age terms by factors of 10 to improve model fit (18). To account for possible differences in fit by race and sex, we will consider using a quadratic curve for BMI in race-sex groups. The model will generate various curves using the maximum likelihood estimates. The most parsimonious model based on the lowest Akaike’s Information Criterion (AIC) will be selected. To account for unequal follow-up time between participants, we will divide the area under the curve by number of follow-up years.

We will evaluate the following measures of adulthood BMI and BMI trajectories:

1. BMI at (visit 4).
2. Percent BMI change in midlife (visits 1 and 4).
3. Percent BMI change in early adulthood (age 25 and visit 1).
4. BMI change in midlife (from linear mixed effects model using BMI from visits 1, 2, 3, and 4)
5. Area under the curve of BMI measurements in midlife (using BMI from visits 1, 2, 3, and 4).
6. Area under the curve of BMI measurements in early adulthood (using BMI from age 25 and visits 1, 2, 3, and 4).
7. Maximum BMI between age 25, and visits 1, 2, 3, and 4.
Outcome:
1. Incident diagnosed diabetes occurring after visit 4. Defined by self-report of a physician diagnosis or glucose-lowering medication use during the annual follow-up telephone calls (19,20).
2. All-cause mortality occurring after visit 4. Vital status of ARIC participants is monitored using annual phone follow-up, community-wide hospital surveillance, and linkage to local and national death registries. Date of death is ascertained by death certificate review.

Covariates:
- Demographic characteristics: age, sex, race-center (white-Minnesota, white-Maryland, white-North Carolina, black-Mississippi, or black-North Carolina), and highest educational attainment (less than high school, high school equivalent, or more than high school).
- Cardiometabolic-related variables at baseline (visit 4): low-density lipoprotein cholesterol (LDL-c, mg/dL), high-density lipoprotein cholesterol (HDL-c, mg/dL), triglycerides (mg/dL), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), use of blood pressure lowering medication (yes or no), medication use for dyslipidemia (yes or no), smoking status (current, former, or never), alcohol use (current, former, and never), and kidney function using estimated glomerular filtration rate (eGFR, mL/min/1.73m²).

Statistical Analysis:
We will describe the distribution of sociodemographic and clinical characteristics by BMI status at baseline (visit 4) and BMI history (categories of BMI change between visits 1-4 and between age 25-visit 1). To evaluate the association between BMI history with incident diabetes and mortality, we will fit Cox proportional hazard models to estimate hazard ratios (HR) and 95% confidence intervals (CIs). The time origin will be visit 4 and the time scale will be years of follow-up. The proportional hazards assumption will be assessed using log-log plots and log-rank tests.

We will fit a series of models to examine the association of BMI and BMI history with diabetes risk and death. Weight status and weight history will be defined using several different exposure variables as described above in the “exposures” section. When evaluating weight history as percent BMI change between two time-points (#2 and #3 above) or BMI change accounting for repeated measurements (#4 above), we will run models with and without adjusting for baseline BMI (visit 4).

Proposed adjustment models:
Model 1: unadjusted
Model 2: demographic characteristics (age, sex, race-center, and highest educational attainment)
Model 3: demographic characteristics plus cardiometabolic-related variables at baseline (visit 4; LDL-c, HDL-c, triglycerides, SBP, DBP, blood pressure medication use, dyslipidemia medication use, smoking status, alcohol use status, and kidney function).
To determine whether or not accounting for weight history will add prognostic value beyond a single measure of BMI, we will compare model fit between the various exposure models. Model fit will be evaluated by comparing the Aikake information criteria (AIC) and the Bayesian information criteria (BIC).

Sensitivity analysis:
In survival analysis, censoring of events should be “non-informative”. Meaning, those who are censored for any reason are assumed to have the same likelihood of developing diabetes as those remaining in follow-up. However, participants who are censored because of death cannot develop diabetes and thus not accounting for death may lead to an overestimate of the true risk. We will address this potential limitation by conducting a competing risk analysis with death using the Fine and Gray approach (Stata procedure: stcrreg) (21).

Potential limitations:
- One self-report measurement of weight is available in early adulthood.
- Self-reported cases of diabetes only (no measurements of glucose after visit 4).
- Residual confounding.
- Only 5 measurements of BMI.

References:
9. Stevens J, Jones DW, Arnett D. Associations of Aging and Birth Cohort with Body Mass Index in a Biethnic Cohort. 2003;11(3).


Cook NR, Rosner BA, Chen W, Srinivasan SR, Berenson GS. Using the area under the curve to reduce measurement error in predicting young adult blood pressure from childhood measures. Stat Med. 2004;23(22):3421–35.


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.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)?

The manuscript proposal most related to the present proposal is the following proposal by Dr. Stevens:

#2471 – June Stevens – Weight change and incident diabetes: The Atherosclerosis Risk in Communities Study

MSP #2471 proposes to elucidate the temporal associations between weight gain, weight loss, and the development of type 2 diabetes. The proposal specifically seeks to evaluate whether poor glucose regulation protects against further weight gain. Dr. Stevens hypothesizes that long-term weight gain (between age 25 and visit 1) and short-term weight loss or maintenance (within three years of diabetes diagnosis) will be associated with increased diabetes risk.

Major distinctions between this proposal and ours are in terms of the research question and approach. Our research question is to determine whether accounting for weight history adds prognostic value above and beyond a single measure of BMI for diabetes risk and mortality. In terms of the approach, Dr. Stevens is evaluating incident diabetes between visits 2 and 4, whereas we propose to evaluate incident diabetes after visit 4. Additionally, in Dr. Steven’s proposal, short-term weight change is assessing the three years before and after diabetes diagnosis. In our proposal, we will use weight history between age 25 and visit 4 but not after diabetes diagnosis.

Dr. Selvin (the senior author on the present proposal) has coordinated the present proposal with Dr. Stevens. Dr. Stevens is included in the author group of the present proposal to help ensure non-overlap and coordination with ongoing work.

Prior ARIC proposals/manuscripts with weight history:

#2254 – Windham – Relationship of Adiposity Trajectories to Later Life Physical Function and Strength

#2196 – Cobb – BMI change and trajectories over 25 years: the relationship between spouse pairs, in the Atherosclerosis in Communities Study
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 http://www.cscu.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.cscu.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.