ARIC Manuscript Proposal #2471

PC Reviewed: 12/9/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Weight change and incident diabetes: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Weight change and incident diabetes

2. Writing Group:

Writing group members: June Stevens
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David Couper
Patrick Bradshaw

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **[JS]**

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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).

Name: David Couper
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3. Timeline:

We plan to submit a manuscript within one year of the approval of this proposal.

4. Rationale:

Type 2 diabetes (T2D) is a leading cause of morbidity and mortality. The prevalence of T2D has increased dramatically in recent years in the United States, and affected about 29.1 million Americans (9.3% of the population) in the year 2012 according to the National Diabetes Statistics Report 2014. Observational studies have consistently shown that excess body weight is among the most important predictors of the onset of T2D [1-3]. In addition, weight loss has been shown to reduce the risk of incident T2D in several clinical trials[4].

Although these associations are well known, the reverse relationship of glucose regulation to changes in weight is less clear. In 1998 Folsom et al. used data from the first 3 examinations of the ARIC cohort to show that a higher fasting insulin concentration was associated with a lower rate of weight gain. The same association was not seen in the younger CARDIA cohort[5]. In 2010 Chiu et al. included the study by Folsom in a review of studies examining the relationship of glucose regulation to changes in weight[6]. Of the 22 studies that met their criteria, 3 reported that poor glucose regulation was associated with weight gain; 12 studies concluded that poor glucose regulation was associated with weight loss and the remaining 7 studies showed null or mixed results. Chui et al. found that all 6 of the studies that focused on diabetic populations unanimously supported a relationship between poor glucose regulation and weight loss or lower levels of weight gain[6]. The authors note that their findings support the view that insulin resistance serves as a homeostatic mechanism to protect against further weight gain. Thus, diabetes appears to be caused by weight gain, but may be a cause of weight loss or reduced weight gain. Elucidation of the temporal sequence of these effects requires longitudinal data with repeated measures of body weight and diabetes status, such as that available in the ARIC cohort.

Studies on the risk of development of diabetes have examined the association of long-term weight change from early to mid- and/or late-adulthood [7], long-term weight change during mid-adulthood [8], or short-term weight change during early-, mid- and late-adulthood [9,10]. We know of no studies that have examined the effects of long-term weight change in early adulthood and short-term weight change in later adulthood surrounding the time of diabetes incidence. We recently published a study using this design and the outcomes of CHD and stroke (not diabetes) in the *American Journal of Epidemiology*[11]. In that work we hypothesized that earlier, long-term weight *gain* would be associated with increased CHD and stroke risk over a long follow-up period. In contrast, we expected later, short-term weight *loss* to be associated with increased risk in the 3 years immediately following the weight change. We found that long-term weight *gain* (since age 25) was associated with elevated CHD and stroke risk compared to weight maintenance; but among middle aged men and women short-term (3-year) weight *loss* of greater than 3% was associated with elevated CHD (HR=1.46) and stroke (HR=1.45) risk within the next 3 years. This elevation in risk tended to be larger in adults who were not dieting to lose weight. We expect to find that the associations between weight change and T2D will also be in opposite directions, depending on the timing of the weight change relative to T2D incidence.

T2D has been associated with both obesity and weight loss. The timing of associations between weight gain, weight loss and the development of diabetes is unclear. The ARIC data provide longitudinal data with which to explore these relations.

5. Main Hypothesis/Study Questions:

The aim of this study is to prospectively evaluate the associations of long-term weight change (change in weight from early-adulthood to mid-adulthood) and short-term weight change (3-year changes in weight during mid-adulthood) with incidence of T2D in mid-adulthood.

We hypothesize that long-term weight gain starting at age 25 (mean period of 30 years) will be associated with increased risk of incident T2D during mid-adulthood; whereas, subsequent short-term weight loss (or reduced weight gain) will be associated with development of T2D. We expect that weight gain in subjects with incident diabetes will be reduced compared to that seen in other subjects both during a 3 year period in which diabetes was diagnosed and during a 3 year period following diabetes diagnosis.

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).

Examination of hazard ratios

We will estimate the HR's for incident diabetes associated with long term weight change and short term weight change between the ARIC visits immediately prior to the interval in which diabetes was diagnosed. We will not use this analytic method to examine weight change during or following the period of diabetes diagnosis because the incidence of the outcome would precede the exposure.

The main study exposures are long-term weight change (change in weight from early-adulthood to mid-adulthood) and short-term weight change (3-year change in weight during mid-adulthood). We will obtain information on these variables from baseline visit (Visit 1) as well as 3 follow-up visits (Visits 2, 3 and 4). We will obtain information about recalled weight at age 25 collected during the baseline visit.

The interval for our studies of long-term weight change begins when the participant was 25 years of age. Given we have information about the age the participants started and age participants stopped smoking, we will be able to derive variable that represents participants' smoking status at age 25. Other relevant covariates for that time period include: age, gender, and race/ethnicity. Additional covariates are also available for ARIC visits during mid to late adulthood including education, physical activity, smoking status, alcohol consumption and diet.

Examination of differences in weight change

We will compare weight change as a continuous variable and in categories between individuals who do and do not develop diabetes. The intervals to be examined include:

a. Age 25 to ARIC baseline
b. 3 year interval between the 2 ARIC visits immediately preceding diabetes incidence
c. 3 year interval between ARIC visits during which diabetes was diagnosed
d. 3 year interval between ARIC visits that directly follow the interval in which diabetes was diagnosed.

Exclusions:

-Participants who had diabetes during the baseline visit 1 (i.e. prevalent cases of diabetes)

-Participants who had CVD or cancer (other than skin cancer) or developed those diseases during the weight change interval being studied or during the interval in which diabetes was diagnosed. They are excluded because these conditions influence weight change.

-Participants with missing data on major outcomes and exposures.

-Following usual ARIC protocol, we will restrict our analysis to two major race groups: African Americans and non-Hispanic whites due to small number of participants from other race/ethnic groups. We will exclude African Americans from Washington County, Maryland, or Minneapolis, Minnesota.

Case Identification:

We will identify incident diabetes cases using definition as follows:

a. Fasting glucose ≥126 mg/dL
   *** For those whose glucose values were from non-fasting state, we will convert the glucose values into fasting-state equivalent values.[13,14]
b. Participants reporting physician diagnosis of diabetes
c. Use of anti-diabetes medications, including oral agents and insulin

We will identify the date of diabetes diagnosis using a linear interpolation method that has been previously published[12]. This same method has been used in several manuscripts with incident diabetes as major outcomes using ARIC data[13,14].

Hazard Ratios:

Cox proportional hazards regression models will be used to model the associations of long-term and short-term weight changes and incident diabetes. The details on weight change calculation and analytical method to address similar type of research question with Coronary Heart Disease and Stroke has been previously published[11]. We will use incident diabetes cases developed any time between Visit 2 and Visit 4 to explore the associations of long-term weight change with diabetes risk. We will exclude T2D cases that occurred within 3 years after the baseline examination (i.e. between visit 1 and visit 2). This will help separate the impact of short-term weight change and allow us to more clearly distinguish the 2 time periods of interest (i.e. long-term vs. short-term weight change).

We will explore the influence of short-term weight change by assessing weight change between Visit 1 and 2, and incident diabetes developed between Visit 2 and 3. Similarly, we will look at the weight change between Visit 2 and 3, and incident diabetes between Visit 3 and 4.

Comparisons of weight change by diabetes status:

Repeated measures analysis using mixed models will be used to examine mean weight change among those who develop diabetes or not in 4 separate analyses examining the relevant intervals described above (under ***Examination of differences in weight change***). We will examine weight change per year and percent weight change per year as continuous variables with the primary exposure incident diabetes in the relevant interval. We may also use multivariate analyses to compare associations between diabetes status and weight change in categories.

Other analyses:

To explore whether the elevated diabetes risk associated with short-term weight loss is related to intentional or unintentional weight loss, we will examine the associations for weight change stratified by self-reported dieting for weight loss and following a diabetic diet. Since diet practices not assessed at every visit these analyses will be limited and exploratory. We plan to use the approach used in our previous work of creating a propensity to diet score[11].

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ 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 __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)?

Stevens J, Erber E, Truesdale KP, Wang C-H, Cai J. **Long- and short-term weight change and incident coronary heart disease and ischemic stroke: the Atherosclerosis Risk in Communities Study.** Am J Epidemiol. 2013 ;178(2):239-48.

Stevens J, Truesdale KP, Wang C-H, Cai J, Erber E. **Body mass index at age 25 and all-cause mortality in whites and African Americans: the Atherosclerosis Risk in Communities study.** J Adolesc Health. 2012 ;50(3):221-7.

Folsom AR, Vitelli LL, Lewis CE, Schreiner PJ, Watson RL, Wagenknecht LE. **Is fasting insulin concentration inversely associated with rate of weight gain? Contrasting findings from the CARDIA and ARIC study cohorts.** IntJObesRelatMetab Disord 1998;22: 48–54.

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.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.

References

(1) Ford ES, Williamson DF, Liu S. Weight change and diabetes incidence: findings from a national cohort of US adults. *Am J Epidemiol.* 1997;146:214-222.

(2) Hu FB, Manson JE, Stampfer MJ et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med.* 2001;345:790-797.

(3) Field AE, Coakley EH, Must A et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. *Arch Intern Med.* 2001;161:1581-1586.

(4) Tuomilehto J, Schwarz P, Lindstrom J. Long-term benefits from lifestyle interventions for type 2 diabetes prevention: time to expand the efforts. *Diabetes Care.* 2011;34 Suppl 2:S210-S214.

(5) Folsom AR, Vitelli LL, Lewis CE, Schreiner PJ, Watson RL, Wagenknecht LE. Is fasting insulin concentration inversely associated with rate of weight gain? Contrasting findings from the CARDIA and ARIC study cohorts. *Int J Obes Relat Metab Disord.* 1998;22:48-54.

(6) Chiu CJ, Wray LA, Beverly EA. Relationship of glucose regulation to changes in weight: a systematic review and guide to future research. *Diabetes Metab Res Rev.* 2010;26:323-335.

(7) de MR, Sun Q, Willett WC, Hu FB, van Dam RM. Overweight in early adulthood, adult weight change, and risk of type 2 diabetes, cardiovascular diseases, and certain cancers in men: a cohort study. *Am J Epidemiol.* 2014;179:1353-1365.

(8) Waring ME, Eaton CB, Lasater TM, Lapane KL. Incident diabetes in relation to weight patterns during middle age. *Am J Epidemiol.* 2010;171:550-556.

(9) Hamman RF, Wing RR, Edelstein SL et al. Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care.* 2006;29:2102-2107.

(10) Delahanty LM, Pan Q, Jablonski KA et al. Effects of Weight Loss, Weight Cycling, and Weight Loss Maintenance on Diabetes Incidence and Change in Cardiometabolic Traits in the Diabetes Prevention Program. *Diabetes Care.* 2014.

(11) Stevens J, Erber E, Truesdale KP, Wang CH, Cai J. Long- and short-term weight change and incident coronary heart disease and ischemic stroke: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol.* 2013;178:239-248.

(12) Duncan BB, Schmidt MI, Pankow JS et al. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. *Diabetes.* 2003;52:1799-1805.

(13) Chow LS, Li S, Eberly LE et al. Estimated plasma stearoyl co-A desaturase-1 activity and risk of incident diabetes: the Atherosclerosis Risk in Communities (ARIC) study. *Metabolism.* 2013;62:100-108.

(14) Chatterjee R, Brancati FL, Shafi T et al. Non-traditional risk factors are important contributors to the racial disparity in diabetes risk: the atherosclerosis risk in communities study. *J Gen Intern Med.* 2014;29:290-297.