ARIC Manuscript Proposal #2035

PC Reviewed: 11/12/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Effect of 3-year weight loss on cardiometabolic risk factors in metabolically healthy obese individuals

b. Abbreviated Title (Length 26 characters): Weight loss in MHO

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. _ZC_ **[please confirm with your initials electronically or in writing]**

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3. Timeline:

Analyses will begin once the manuscript proposal is approved.

4. Rationale:

Excess weight is a primary public health concern since approximately one-third of the adult population in the United States have a body mass index ≥ 30 kg/m^2 [1]. Excess weight is a well-established risk factor for heart disease [2], diabetes[2], several types of cancer [3] and mortality [4] which is believed to be due to its effects on dyslipidemia, insulin resistance and chronic systemic inflammation [5]. Correspondingly, weight loss is well-evidenced in reducing chronic disease risk factors related to excess weight and is therefore recommended by major health agencies [6].

Recent studies have found that around 30% of obese individuals have relatively normal cardiometabolic profiles [7], including normal blood pressure and lipid profiles, and a high degree of insulin sensitivity [8]. These metabolically healthy but obese (MHO) individuals are characterized by a more favorable fat pattern (such as less visceral fat [9] and smaller waist circumference [8]), certain lifestyle factors (such as higher physical activity level [8]) and higher fitness [10], compared to those who are metabolically unhealthy but obese (MUO). Although metabolically healthy obesity may not be a stable condition [11,12], exposure to these characteristics may convey a favorable long-term health consequence. A recent study found that MHO participants were not at increased risk of cardiovascular disease and all-cause mortality over a 7-year follow-up compared to metabolically healthy normal weight (MHNW) participants [13]. The discrepancies in disease risks between obesity phenotypes indicate that they may respond differently to excess weight, which suggests that they may respond differently to weight loss. However, most of previous studies on which weight loss recommendations were based did not discriminate metabolic health - obesity phenotypes.

There are only limited experimental studies that examined the short-term (3-9 months) effect of diet- [14-18] or/and exercise- [16,17] or gastric banding-induced [19] weight loss on cardiometabolic risk factors by obesity phenotypes. As expected, all these studies reported weight loss had favorable effects in MUO participants. In contrast, inconsistent results were reported in the relative and absolute cardiometabolic benefit from weight loss in MHO participants. Sesti et al. reported similar effects with MUO participants [19], another two studies reported significant but smaller improvement than MUO participants [17,18], while another two studies found no significant improvement [14,16]. Karelis et al. reported a decrease in insulin sensitivity measured by the euglycaemic–hyperinsulinaemic clamp technique, in MHO postmenopausal women in response to a 6-month energy-restricted diet [15]. In addition, no study has examined the effect of weight loss on cariometabolic risk factors in free-living MHO people over a longer period of time.

The goal of the proposed study is to prospectively examine whether obesity phenotypes respond to weight loss differently in terms of cardiometabolic risk factors, and to examine whether weight loss clinically significantly improves cardiometabolic risk factors in MHO middle-age adults over a 3-year period.

5. Main Hypothesis/Study Questions:

Aim 1: Do MHO individuals respond differently to weight loss compared to MUO individuals?

Hypothesis 1: For a similar weight loss between visits, MHO individuals will undergo a smaller decline compared to MUO individuals in the levels of triglycerides (TG), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (FBG), fasting insulin (FI) and insulin resistance determined by homeostasis model assessment (HOMA-IR), and a smaller increase in high density lipoprotein cholesterol (HDL-C).

Aim 2: Is weight loss associated with a change in cardiometabolic risk factors among MHO individuals?

Hypothesis 2a: Among MHO individuals, weight loss between visits will be associated with a decrease in the levels of TG, SBP, DBP, FBG, FI and HOMA-IR, and an increase in HDL-C.

Hypothesis 2b: MHO individuals who lose weight between visits will have lower levels of TG, SBP, DBP, FBG, FI and HOMA-IR, and a greater level of HDL-C compared to MHO individuals who maintained their body weight over the same interval of time.

Hypothesis 2c: For a given weight loss between visits, MHO individuals, compared to MHNW individuals, will have lower TG, SBP, DBP, FBG, FI and HOMA-IR, and greater HDL-C at the end of interval between visits.

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).

Study Design: We will use a prospective cohort study design to address the research questions. A "stacked" data set will be created by treating each 3-year interval (between visit 1-2, 2-3 and 3-4) for each participant as a separate observation.

Aim 1 will be addressed by comparing changes in cardiometabolic risk factors in MHO individuals who lost weight with MUO individuals who lost weight between visits.

Aim 2a will be addressed by a paired analysis to compare cardiometabolic risk factors between visits in MHO group who lost weight over the same interval.

Aim 2b will be addressed by comparing changes in cardiometabolic risk factors between MHO group who lost weight and MHO group who maintained weight between visits.

Aim 2c will be addressed by comparing changes in cardiometabolic risk factors between MHO group who lost weight and MHNW group who lost weight between visits.

Variable definitions:

1) Body weight status will be defined using body mass index recommended by the World Health Organization (as normal weight: 18.5 - 24.9 kg/m^2, obesity: ≥ 30 kg/m^2) [23].
2) For each 3-year interval, the percent weight change will be calculated as weight at the end of an interval minus weight at the beginning of the interval then divided by the weight at the beginning of the interval. Weight loss will be defined as < -3 percent weight change, weight maintenance will be defined as weight change ≥ -3 and ≤ 3 percent weight change [24].
3) Metabolically healthy will be defined as meeting 0 of the criteria for metabolic syndrome except waist circumference by National Cholesterol Program's Adult Treatment Panel-III (ATP-III) guidelines: elevated TG: ≥ 150 mg/dL; low HDL-C: < 40 mg/dL for men and < 50 mg/dL for women; elevated blood pressure: ≥ 130/≥ 85 mmHg; elevated FBG: ≥ 110 mg/dL [25].
4) Insulin sensitivity will be evaluated using homeostasis model assessment (HOMA-IR): fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5 [26].

Outcome variables: TG, HDL-C, SBP, DBP, FBG, FI and HOMA-IR. All these outcome variables will be treated as continuous.

Covariates: Covariates for the analysis will include: age at the beginning of each interval, gender, research center, race, education, smoking, alcohol consumption, physical activity, elapsed time between visits, weight at the beginning and the end of each interval.

Inclusion/Exclusion Criteria:

Inclusion criteria:

Aim 1: only MHO individuals who lost weight and MUO individuals who lost weight over any 3-year interval will be included in the analysis.

Aim 2a: only MHO individuals who lost weight over any 3-year interval will be included in the analysis.

Aim 2b: only MHO individuals who lost weight and MHO individuals who maintained weight over any 3-year interval will be included in the analysis.

Aim2c: only MHO individuals who lost weight and MHNW individuals who lost weight over any 3-year interval will be included in the analysis.

Exclusion criteria:

Among those who match the inclusion criteria:

- Those who were taking medicine that affects the levels of outcome variables will be excluded for pertinent analysis.

- Those who had diabetes, heart disease, stroke, or cancer at the beginning or the end of an interval will be excluded from all analyses.
- The 3-year interval between visits will be excluded from the analysis if any variable in the model is missing at the beginning or the end of an interval.

Statistical Analysis:
Mixed models (PROC MIXED procedure in SAS software, version 9.2; SAS Institute, Inc., Cary, North Carolina) will be used to account for the within-subject correlation due to multiple observations per subject. The change between visits or level at the end of the 3-year interval for individual cardiometabolic risk will be treated as continuous dependent variable. The LSMEANS option will be used with the PROC MIXED procedure (SAS Institute, Inc.) to estimate the adjusted mean 3-year change (between visits) in cardiometabolic risk factors for each group and to determine whether there were significant differences in the magnitude and direction of the changes between groups.

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)?

MS#815 The associations between weight maintenance and metabolic risk factors for cardiovascular disease.
MS#828 Beneficial Effects of 5 -15% Weight Loss on Metabolic Risk Factors for Type 2 Diabetes and Cardiovascular Disease.
Above the two studies respectively examined the effect of weight maintenance and weight loss on metabolic risk factors in African American and white adults. In contrast, our analysis will focus on the effect of weight loss on metabolic risk factors in a subgroup of the ARIC sample: metabolically healthy but obese people.

MS#1680 Longitudinal patterns and determinants of metabolic subtypes of obese, overweight and normal weight individuals
Above the study examined the prevalences of obesity phenotypes at ARIC baseline visit, and prospectively examined the association between sociodemographic factors and lifestyle behaviors and the transition from MHO to MUO. Our analysis will focus on the effect of weight loss on metabolic risk factors.

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. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA 2012;307:491-7.

2. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. JAMA 1999;282:1523-9.

3. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625-38.

4. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. JAMA 2005;293:1861-7.

5. Gutierrez DA, Puglisi MJ, Hasty AH. Impact of increased adipose tissue mass on inflammation, insulin resistance, and dyslipidemia. Curr Diab Rep 2009;9:26-32.

6. Donnelly JE, Blair SN, Jakicic JM, et al. American College of Sports Medicine Position Stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. Med Sci Sports Exerc 2009;41:459-71.

7. Karelis AD, St-Pierre DH, Conus F, Rabasa-Lhoret R, Poehlman ET. Metabolic and body composition factors in subgroups of obesity: what do we know? J Clin Endocrinol Metab 2004;89:2569-75.

8. Wildman RP, Muntner P, Reynolds K, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). Arch Intern Med 2008;168:1617-24.

9. Brochu M, Tchernof A, Dionne IJ, et al. What are the physical characteristics associated with a normal metabolic profile despite a high level of obesity in postmenopausal women? J Clin Endocrinol Metab 2001;86:1020-5.

10. Ortega FB, Lee DC, Katzmarzyk PT, et al. The intriguing metabolically healthy but obese phenotype: cardiovascular prognosis and role of fitness. Eur Heart J 2012;.

11. Bradshaw PT, Monda KL, Stevens J. Metabolic Syndrome in Healthy Obese, Overweight, and Normal Weight Individuals: The Atherosclerosis Risk in Communities Study. Obesity (Silver Spring) 2012;.

12. Hwang LC, Bai CH, Sun CA, Chen CJ. Prevalence of metabolically healthy obesity and its impacts on incidences of hypertension, diabetes and the metabolic syndrome in Taiwan. Asia Pac J Clin Nutr 2012;21:227-33.

13. Hamer M, Stamatakis E. Metabolically healthy obesity and risk of all-cause and cardiovascular disease mortality. J Clin Endocrinol Metab 2012;97:2482-8.

14. Shin MJ, Hyun YJ, Kim OY, Kim JY, Jang Y, Lee JH. Weight loss effect on inflammation and LDL oxidation in metabolically healthy but obese (MHO) individuals: low inflammation and LDL oxidation in MHO women. Int J Obes (Lond) 2006;30:1529-34.

15. Karelis AD, Messier V, Brochu M, Rabasa-Lhoret R. Metabolically healthy but obese women: effect of an energy-restricted diet. Diabetologia 2008;51:1752-4.

16. Kantartzis K, Machann J, Schick F, et al. Effects of a lifestyle intervention in metabolically benign and malign obesity. Diabetologia 2011;54:864-8.

17. Janiszewski PM, Ross R. Effects of weight loss among metabolically healthy obese men and women. Diabetes Care 2010;33:1957-9.

18. McLaughlin T, Abbasi F, Lamendola C, et al. Differentiation between obesity and insulin resistance in the association with C-reactive protein. Circulation 2002;106:2908-12.

19. Sesti G, Folli F, Perego L, Hribal ML, Pontiroli AE. Effects of weight loss in metabolically healthy obese subjects after laparoscopic adjustable gastric banding and hypocaloric diet. PLoS One 2011;6:e17737.

20. Truesdale KP, Stevens J, Cai J. Effect of 3-year weight history on blood pressure: the atherosclerosis risk in communities study. Obesity (Silver Spring) 2008;16:1112-9.

21. Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL. Overweight and obesity in the United States: prevalence and trends, 1960-1994. Int J Obes Relat Metab Disord 1998;22:39-47.

22. Karelis AD. Metabolically healthy but obese individuals. Lancet 2008;372:1281-3.

23. Anonymous WHO Obesity: preventing and managing the global epidemic. Report on a WHO Consultation on Obesity, Geneva, 3–5 June, 1997. WHO/NUT/NCD/98.1. Technical Report Series Number 894World Health Organization, Geneva (2000).

24. Stevens J, Truesdale KP, McClain JE, Cai J. The definition of weight maintenance. Int J Obes (Lond) 2006;30:391-9.

25. Grundy SM, Brewer HB,Jr, Cleeman JI, et al. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004;109:433-8.

26. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.