ARIC Manuscript Proposal # 1436

1.a. **Full Title**: Mediation of effects of obesity on coronary heart disease in a bi-ethnic cohort: the Atherosclerosis Risk in Communities (ARIC) Study

b. **Abbreviated Title (Length 26 characters)**: Mediation of obesity-CHD

2. **Writing Group**: Jill McClain, Cathy Zimmer, Eric Whitsel, Linda Adair, Kimberly Truesdale, June Stevens (This research will be performed as part of the lead author’s doctoral dissertation.)

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___JM_____ [please confirm with your initials electronically or in writing]

**First author**: Jill McClain  
**Address**: Department of Nutrition  
CB# 7461  
University of North Carolina  
Chapel Hill, NC 27599  

Phone: 919-843-5246  
Fax: 919-966-7216  
E-mail: jillmccl@unc.edu

**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**: June Stevens  
**Address**: Department of Nutrition  
CB# 7461  
University of North Carolina  
Chapel Hill, NC 27599  

Phone: 919-966-7218  
Fax: 919-966-7216  
E-mail: june_stevens@unc.edu

3. **Timeline**: Work will begin immediately.

4. **Rationale**:  
Excess adiposity is associated with risk factors for coronary heart disease (CHD), including high blood pressure, elevated glucose and dyslipidemia. Although many studies have examined the relationship between obesity and these CHD risk factors, and between these risk factors and CHD events, few have analyzed mediation of the obesity-CHD relationship by individual risk factors, and even fewer have compared mediation across risk factors. The lack of studies comparing risk factors as mediators is due, in part, to the scarcity of appropriate data on both measured metabolic mediators and CHD outcomes and, in
part, to the limitations of traditional epidemiologic methods for this purpose. Mediation is commonly analyzed in other fields using structural equation modeling (SEM). SEM has several advantages over standard regression for analyses of mediation, including the specification of each path (and importantly, each non-path) among all variables in a given model and the ability to explicitly model the measurement error of variables. In particular, SEM permits significance-testing of the indirect (mediated) effect.

We know of no studies that have assessed racial and gender differences in the mediation of CHD. Racial and gender differences have been found in the prevalences of obesity, CHD risk factors and CHD outcomes, as well as in the associations among these variables, but it is not clear whether risk factors mediate the adiposity-CHD relationship to the same degree across race and gender. For example, African American women have a higher incidence of CHD than White women, as well as a higher average body mass index (BMI) and higher blood pressure, but is the higher incidence of CHD due to the effects of increased obesity on blood pressure, or are these health issues less associated with each other in African American women?

A comparison of effects of obesity on CHD through blood pressure, glucose and lipids must consider how to incorporate medication use. Therefore we will explore this topic in order to inform our primary analyses and to better understand the impact of medications.

5. Main Hypothesis/Study Questions:
1. Primary Aim – Examine and compare the role of metabolic risk factors as mediators of the relationship between obesity (BMI and waist circumference) and time to CHD in a bi-ethnic cohort. Structural equation modeling will be used to examine the following metabolic risk factors: systolic and diastolic blood pressure, glucose, LDL and HDL cholesterol and triglycerides. Obesity measures will be BMI and waist circumference.
1.a. Examine and compare metabolic risk factors individually as mediators of the effect of obesity on CHD
1.b. Examine and compare metabolic risk factors in combination as mediators of the effect of obesity on CHD
1.c. Determine if mediation of the obesity-CHD relationship differs by race and/or gender

2. Secondary Aim – Explore how antihypertensive, lipid-lowering and diabetes medications affect mediation of the obesity-CHD relationship

Hypotheses are presented in the methods section because some of the tests to be used are explained there.

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).

Primary Aim

Examine and compare the role of metabolic risk factors as mediators of the relationship between obesity (BMI and waist circumference) and time to CHD in a bi-ethnic cohort.

The metabolic risk factors to be studied include: systolic and diastolic blood pressure, glucose, LDL cholesterol, HDL cholesterol and triglycerides. Analyses of glucose and lipids will be limited to a fasting sample.
Software – Mplus

Analyses will be performed using Mplus statistical software. Mplus is a software package that can be used for a variety of analyses, including linear and logistic regression, multi-level modeling, survival analysis, factor analysis and structural equation modeling.

**Aim 1a:** Examine and compare metabolic risk factors individually as mediators of the effect of obesity on CHD.

Exposures will be continuous BMI and waist circumference at baseline. Final models for Aims 1a-c will depend on the strategy for addressing medication use determined by the analyses proposed in Aim 2. Using Cox proportional hazard regression in conjunction with a structural equation model, we will test the models with and without each mediator (Figure 1 shows the schematic model with the mediator; Figure 2 shows the structural model with LDL cholesterol as the mediator). We will test overall model fit and the significance of the direct and indirect path coefficients between BMI/waist and CHD hazard.

We hypothesize that:

- Obesity (BMI and waist) will be directly and positively associated with CHD hazard, as indicated by a significant positive direct path coefficient when no mediators are included in the model.
- Each metabolic risk factor will be a significant mediator of the obesity-CHD relationship, as indicated by a significant indirect effect, calculated as the product of the two indirect path coefficients ($\gamma_{11} \times \beta_{21}$).

**Figure 1**

**Figure 2**
**Aim 1b:** Examine and compare risk factors in combination as mediators of the effect of obesity on CHD.

Variables and analyses will be the same as in Aim 1a, but with mediators combined in logical groups. We will test models for blood pressure and lipids as shown in Figure 3 (e.g., the model with lipid variables grouped together), as well as with all mediators together (not shown). (Note that the mediators are intercorrelated, but the arrows showing the intercorrelation have been removed to make the figure easier to read.) We will test overall model fit and the significance of the direct and indirect path coefficients between BMI/waist and CHD hazard.

We hypothesize that:
- Each individual metabolic risk factor will be a significant mediator of the obesity-CHD relationship, as indicated by a significant indirect effect, calculated as the product of the two indirect path coefficients.

**Aim 1c:** Determine if mediation of the obesity-CHD relationship differs by race and/or gender.

We will repeat the analyses in aims 1a and 1b with the population grouped by race and gender. We will compare overall fit of the mediation model in each race-gender group using appropriate model fit indices. We will also compare the path coefficients and the mediation effects.

We hypothesize that:
- The mediation models will demonstrate a better overall fit (will explain more of the variance in time to CHD) in Whites than in African Americans.
- Mediation, as measured by the product of the indirect path coefficients, will be less in African Americans than in Whites.

**Secondary Aim**

*Explore how antihypertensive, lipid-lowering and diabetes medications affect mediation of the obesity-CHD relationship.*

Variables will be the same as in Aim 1a, but with the addition of three binary medication variables. We will explore the effects of stratifying the models in Aim 1a on relevant medication use and of imputation strategies for the value of the mediator in treated participants.²

We hypothesize that:
- The indirect effects (product of the path coefficients) of obesity on CHD through mediators will be less in persons on relevant medications than in those not on such medications.
- When an appropriate imputation strategy is used to account for the effects of medication on the mediator, the indirect effects will not be different in the two medication groups.

If the second hypothesis is supported for a given mediator, we will retain that imputation strategy in all models involving that mediator and will combine the treated and untreated subjects in subsequent analyses. If mediation is still different between groups, then we will continue to present results stratified by medication use.
Limitations:
- Since subjects are not randomized to exposure, there is potential for uncontrolled confounding of the relationship between adiposity, metabolic risk factors and CHD, perhaps by unmeasured or poorly measured socioeconomic or other variables.
- If we conclude from the secondary analysis that we should stratify primary analyses on medication status, we will have lower power to detect differences in mediation by racial group.

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  ___ 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)?

MS343 - Insulin, NIDDM, Obesity, & CHD Incidence
and
MS343A - Body mass index, waist/hip ratio, and coronary heart disease incidence in African Americans and whites
Lead: A. Folsom
and

MS611 - ARIC CHD Risk Prediction
Lead: Chambless, LE
MS683 - Obesity and concomitant risk for cardiovascular disease: implications of obesity Guidelines
Lead: Marion R. Wofford, M.D.

MS703 - Estimation of the causal effect of risk factor modification on mortality and incidence of CHD and stroke
Lead: K. Tilling

MS832 - Prediction of subclinical atherosclerosis, incident CHD, and all-cause mortality using recently published definitions of the metabolic syndrome
Lead: Annie McNeill, MPH

MS911 - The Association of Overweight and Obesity with Incident Coronary Heart Disease is Attenuated by Adjustment for Markers of Inflammation and Endothelial Dysfunction
Lead: J. Shawn Miles, M. D.

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.csc.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.