ARIC Manuscript Proposal # 1177

PC Reviewed: _08__/_15__/06	**Status: __A___**	**Priority: __2__**
SC Reviewed: _08__/_17__/06	**Status: __A__**	**Priority: __2__**

1.a. Full Title: The association of hip circumference and metabolic diseases: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Hip circumference and disease

2. Writing Group:

Writing group members: Emily Parker, Mark Pereira, June Stevens, Darin Erickson, Aaron Folsom

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

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3. Timeline: we plan to complete the analysis and manuscript in one year

4. Rationale:

The prevalence of obesity has been increasing in recent decades [1-4]. Increases in overweight and obesity are an important public health problem because of increased risk of diabetes, cardiovascular diseases and certain cancers [2, 5]. Relative bodyweight and overweight/obesity status is often measured as the body mass index (BMI) in epidemiological

studies. However, body composition, in particular body fat distribution, may be even more important for predicting disease risk than overall bodyweight [6, 7]. Intraabdominal (visceral) fat may be the most detrimental form of excess body fat because it is thought to be of significant etiologic importance to the development or exacerbation of insulin resistance, giving rise to a variety of metabolic risk factors for diabetes mellitus and cardiovascular disease [8-11].

Based on its metabolic importance, assessment of visceral fat has been a high priority in studies of diabetes mellitus and CVD epidemiology. There are several methods available to measure abdominal fat. Visceral fat can be measured by computed tomography (CT), magnetic resonance imaging (MRI), or dual energy X-ray absorptriometry (DEXA), but the relatively high cost and time commitment usually makes these methods impractical for large cohort studies. In epidemiological studies, methods for assessing abdominal fat include waist circumference as a marker of total abdominal fat and waist-to-hip circumference ratio (WHR) as a marker of body fat distribution. Waist circumference is highly correlated with more direct measures of visceral fat [12, 13]. A high WHR indicates a high proportion of abdominal fat to lower body fat/mass [12, 13].

Whereas the waist circumference, as in independent disease risk marker, has been of interest for some time. Increasingly investigators have begun to explore the hip circumference as a possible predictor of chronic disease risk, independent of waist and body mass index. If abdominal fat is taken into account, then greater hip circumference may reflect lower body composition to some degree. Specifically, hip circumference may be used as a surrogate measure for two general body tissues of relevance to chronic disease risk in the gluteofemoral region -- lean mass (muscle and bone) and subcutaneous fat mass [14, 15]. That is, if larger hips are reflective of lean mass, in addition to or independent of fat mass, this may also be important because of the known benefits of muscle mass on glucose uptake [15-17]. Furthermore, narrow hips may indicate muscle loss, particularly among older adults, with a number of deleterious ramifications for health risks [16, 18-20]. A recent extensive review on this topic by Freedland suggested that subcutaneous fat accumulation on the hips and legs may protect against atherosclerosis and metabolic syndrome [21]. Subcutaneous fat differs from visceral fat in a number of ways. Compared to visceral fat, subcutaneous fat has low levels of basal lipolysis and lipolytic stimulation, thus potentially reducing the release of free fatty acids into the bloodstream [22]. By contrast, there is free fatty acid flux directly from visceral fat into hepatic circulation, a likely mechanism for the insulin resistance and dyslpidemia associated with large visceral fat depots [8, 23]. In addition, subcutaneous fat may consist of relatively small adipocytes that are less prone to insulin resistance and may act as a buffer for circulating fatty acids [21, 24, 25].

In addition to the number of interesting unique metabolic features of the hip mass or circumference, there are also a few statistical concerns that provide further rationale for examining the hip circumference as an independent risk marker of disease. When waist and hips are combined in the waist-hip ratio, properties unique to adipose and lean compartments cannot be independently evaluated, a potentially important limitation in much of the literature to date regarding body composition and diabetes and CVD etiology. Additionally, a ratio prohibits the examination of nonlinear associations between the numerator (waist) and denominator (hip) [26].

There is accumulating evidence for possible independent associations between hip circumference and disease risk in the recently published epidemiologic literature [15, 27-37]. Hip circumference is inversely associated with CVD morbidity and mortality in several studies [28, 29, 38]. Of the studies that have specifically examined the associations of hip circumference with metabolic diseases (see Table 1) most were cross sectional [15, 27, 31, 33-35, 37, 39]. The few prospective studies had small sample sizes and/or short follow-up times [28, 29, 32]. Yusuf et al, in a large case control study from the INTERHEART study, observed a strong inverse association between hip circumference and odds for myocardial infarction, with and odds ratio of 0.76 (95% CI 0.67-0.86) for those in the highest v. lowest quintile of hip circumference after adjusting for age, sex, smoking, BMI and waist circumference (there was no association before adjusting for BMI and waist) [36]. In a 6-year prospective analysis of the Hoorn study, when hip circumference was

modeled alone, there was no significant association in men or women; after adjusting for age, BMI, and waist circumference a 1 SD increment in hip circumference was associated with an odds ratio for developing diabetes of 0.55 (95% CI 0.36-0.85) in men and 0.63(95% CI 0.42-0.94) in women [32]. A final prospective study from the Danish MONICA project reported that larger hip circumference, relative to BMI and waist circumference, predicted lower incidence of CVD and CHD over ten years of follow-up in men and women, and, for women only, lower total mortality rates over thirteen years [28]. It is important to note that none of the published studies reported null associations or direct associations between hip circumferences and the outcomes, raising the possibility of publication bias.

The Atherosclerosis Risk in Communities Study offers a unique opportunity to examine associations of hip circumference and chronic disease in a biethnic cohort of men and women as they progress from middle-aged to older adults. Few prospective studies have looked at hip circumference as an **independent** predictor of metabolic diseases including diabetes and coronary heart disease. These studies all had small sample sizes relative to ARIC. Furthermore, we found no published studies that included repeated measures of hip circumference. ARIC has the added advantage of repeated measures, allowing the assessment of changes in body measures over time, an important study design characteristic relevant to aging and chronic disease. The proposed study will examine prospectively the association of hip circumference with metabolic diseases, diabetes and coronary heart disease in a biethnic cohort of black and white men and women.

Table 1. Published articles on independent associations* of hip circumference (HC) and metabolic disease.

Authors	Year	Study Design	Endpoint of interest	Findings for associations of HC and endpoints*
Snijder et al [33]	2003	Cross sectional	Glucose tolerance	Inverse association in men and women
Snijder et al [34]	2004	Cross sectional	Metabolic syndrome	Inverse association in 4 ethnic groups
Snijder et al [35]	2004	Cross sectional	Metabolic syndrome	Inverse association
Seidell et al [30]	1997	Cross sectional	Diabetes prevalence	Smaller hips associated with higher diabetes prevalence
Hartz et al [37]	1984	Cross sectional	Diabetes, hypertension prevalence	Inverse association associated with lower prevalence of disease in women
Benetou et al [27]	2006	Cross sectional	Blood lipids	Inverse association in women
Seidell et al [31]	2001	Cross sectional	CVD risk factors	Narrow HC associated with low HDL-C, high glucose and insulin concentrations
Yusuf et al [36]	2005	Case Control	MI risk	Inverse association
Snijder et al [32]	2003	Longitudinal	Incident diabetes	6 years of follow-up, inverse association in 1,357 men and women
Heitmann et al [28]	2004	Longitudinal	CVD morbidity and mortality	13 years of follow-up, large HC was associated with reduced risk in 1,446 women, but not in 1,514 men
Lissner et al [29]	2001	Longitudinal	CVD mortality, Total mortality	24 years of follow-up, inverse association in 1,404 Swedish women

* Adjusted for waist circumference and body size in statistical models.

5. Main Hypothesis/Study Questions:

Aims and hypotheses. The overall objective of this study is to examine the association of hip circumference and metabolic diseases -- diabetes and coronary heart disease -- in a biethnic cohort of men and women.

Aim 1. To examine the association of hip circumference and risk of incident diabetes in a biethnic cohort of men and women.

Hypothesis 1. Individuals with larger hip circumference will have a reduced risk of incident diabetes compared to those with smaller hip circumference, adjusted for waist circumference and other available measures.

Aim 2. To examine the association of hip circumference and incident coronary heart disease in a biethnic cohort of men and women.

Hypothesis 2. Individuals with a larger hip circumference will have a reduced risk of CHD incidence compared to those with a smaller hip circumference, adjusted for waist circumference and other available measures.

- Incident diabetes
- Incident CHD

Medical History (prevalent at baseline)
- Diabetes
- CHD
- Hypertension
- Stroke
- Cancer

Others
- Smoking status and # cigarettes
- Physical activity
- Alcohol use
- Dietary intakes

Exclusions
- Ethnicity other than white or African-American
- African-Americans in Minnesota or Maryland
- Diabetic at baseline
- Prevalent CHD at baseline
- Missing anthropometric data
- Non fasting

Analysis Plan:

In order to assess independent association of hip circumference with disease, hip circumference and other measures of body size must be included in the same model. A potential limitation to this modeling strategy is that measures of body size may pose collinearity problems in statistical modeling. However, of the studies described above only a small number addressed this issue [27, 28, 31, 38]. One approach to avoid the problem with collinearity of body circumferences/ measures is to use the residuals of hip and waist circumferences simultaneously in regression models [40]. Residual analyses are a relatively simple way to evaluate independent contributions of highly-correlated parameters. However, only a few of these studies used the residuals of hip and waist circumference in models predicting disease [27, 28, 31].

I. Exploratory data analysis of body circumferences
   a. Plots and histograms of body circumference data will be used to examine the structure of the data prior to conducting analyses with residuals
   b. Compute predicted values (residuals)
   c. Plots and histograms of the residuals will also be examined
II. Pearson correlation of anthropometric measures
III. Descriptive characteristics (mean and standard deviation or percent) by hip circumference quantiles at baseline
   a. Demographic factors
   b. Behavioral factors (smoking status, alcohol use, dietary intakes, sport activity index)
   c. Anthropometric measures
   d. Other risk markers for metabolic diseases

Aim 3. To examine associations of hip circumference and risk factors for metabolic disease in a biethnic cohort of men and women.

Hypothesis 3. Larger hip circumference will be inversely associated with markers of glucose and insulin metabolism, including fasting insulin, triglycerides, HDL-cholesterol (positive association), CRP, and blood pressure, adjusted for waist circumference and other available measures.

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).

Data to be used for prospective analyses:

Identification information
- Participant identification number
- Visit date
- ARIC field center

Demographics
- Age
- Date of birth
- Ethnicity
- Sex
- Education

Anthropometry
- Weight
- Height
- BMI
- Waist circumference
- Hip circumference
- Waist to hip ratio

Metabolic risk markers
- Systolic blood pressure
- Diastolic blood pressure
- Antihypertensive medication use
- Fasting insulin
- Fasting glucose

- Fasting status
- Triglyceride
- HDL cholesterol
- LDL cholesterol
- CRP

Metabolic disease endpoints

IV. To test Hypotheses 1 and 2, we will model diabetes and CHD incidence longitudinally logistic regression and proportional hazards models using residuals of hip and waist circumferences obtained from linear regression models. Models will be sex specific.
   a. Construct models with residuals
   b. Adjusted for age, BMI and waist and hip circumferences continuously
   c. Add a quadratic term for body girth measurements (hip and waist separately) to look for a non-linear relationship between body girth and outcome variables
   d. If there is not a linear relationship, then model body girth as quartiles
   e. Adjust for other possible confounding variables including SES, race, dietary intakes (Keys' score, cereal fiber, fruit and vegetables), smoking status, pack years, estrogen therapy, alcohol consumption, menopause and hormone use in women
   f. Finally adjust for possible upstream or mediating/ causal pathway variables including physical activity

V. To test Hypothesis 3, we will examine cross sectional and prospective associations of hip circumference and metabolic disease risk markers
   a. Cross sectional
      i. Correlations of hip circumference and metabolic disease risk markers
      ii. Linear regression analyses of hip circumference and metabolic disease markers adjusted for age BMI, waist and hip continuously
   b. Prospective
      i. Mixed models to assess means for risk markers over follow-up stratified by hip quantile
      ii. Quantify change in risk markers over time using mixed regression models
      iii. Determine incidence of development of metabolic risk markers among individuals without risk factors at baseline

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 ICTDER02 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 ICTDER02 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 ICTDER02 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 following published research articles and ARIC manuscript proposals are the most closely related. While they each look at associations of body habitus with metabolic diseases none of them examine associations of hip circumference with outcomes independent of waist circumference and BMI.

Published articles:
Folsom, AR et al., Body mass index, waist/hip ratio, and coronary heart disease incidence in African Americans and whites. Atherosclerosis Risk in Communities Study Investigators. *Amer J Epidemiol* 1998;148(12):1187-94.

Harris, MM et al., Associations of fat distribution and obesity with hypertension in a bi-ethnic population: The ARIC study. *Obesity Research* 2000;8(7):516-524.

Stevens, J et al., Sensitivity and specificity of anthropometrics for the prediction of diabetes in a biracial cohort. *Obesity Research* 2001;9(11):696-705.

Manuscript proposals:
#710 June Stevens, Associations between changes in anthropometric variables and mortality
#711 June Stevens, Obesity and fat patterning as predictors of mortality

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. primiarly 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/

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.

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