ARIC Manuscript Proposal # 1708

PC Reviewed: 6/14/11  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Interaction between a multi-factorial diet score and genetic loci for body mass index (WHR) and waist:hip ratio (WHR)

b. Abbreviated Title (Length 26 characters): BMI & WHR loci x diet score

2. Writing Group:
Writing group members: Tentative list below; additional authors will be added; other ARIC investigators are welcome

<table>
<thead>
<tr>
<th>PARTICIPATING COHORT</th>
<th>N</th>
<th>PHENOTYPE ANALYST (if applicable)</th>
<th>MAIN ANALYST</th>
<th>AUTHOR (cohort lead)</th>
<th>AUTHOR 2</th>
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<th>AUTHOR 4</th>
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<th>AUTHOR (cohort senior)</th>
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<td>Emily Sonestedt</td>
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<td>Marju Orho-Melander</td>
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _JN_ [please confirm with your initials electronically or in writing]

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E-mail: jennifer.a.nettleton@uth.tmc.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: AS LISTED ABOVE

3. Timeline: 
   Cohort-specific data analyses: July 15, 2011
   Meta-analysis: August 15, 2011
   Manuscript drafting complete: October 1, 2011

4. Rationale:
The prevalence of overweight and obesity has increased significantly in recent decades. Inarguably, this epidemic is among the most important public health challenges faced today. Overweight and obesity significantly increase the risk of multiple chronic diseases, and morbidity management alone places substantial burdens on our health care systems. Obesity is thought to be largely the result of environmental factors that drive inactivity and over-consumption. However, several studies have shown that multiple genetic loci may also play a part in determining body weight and body composition (1-8). However, the rapid rises in prevalences of overweight and obesity argue against a solely genetic etiology. Risk is more likely determined by interplay between genes and environmental factors (9), factors which have changed dramatically in recent decades.

Recent meta-analyses of multiple, large GWAS have identified 32 genetic loci related to body mass index (BMI) (1) and 14 loci related to waist-to-hip ratio (WHR) (8). These regions provide insight into the biological mechanisms that underlie body composition-related traits. The current project proposes to utilize these findings to determine whether dietary factors—specifically dietary patterns consistent with public health recommendations and scientific research in the context of cardiometabolic disease—augment or ameliorate the effects of these polymorphic regions on body size/composition.

5. Main Hypothesis/Study Questions:

- **STEP 1: Diet Score main “effect”**: Determine the magnitude of the association of the CHARGE-Nutrition-Working-Group-defined “Healthy Diet Score” with body mass index (BMI) and waist-to-hip ratio (WHR).
  - Models will be adjusted for other lifestyle factors to better isolate the associations of diet from those of other healthy behaviors.
  - Models will be run separately for each outcome in the full cohort and in each men and women separately.

  ➔ **DATA SHARING TARGET FOR STEP 1: JUNE 15**

- **STEP 2: Diet Score x genetic risk interaction**: Determine whether a higher Healthy Diet Score mitigates (or a low score amplifies) the BMI- and/or WHR-raising effect of SNPs identified in previous GWAS for BMI and WHR. (Speliotes 2010 and Heid 2010)
  - To minimize the number of statistical tests, we will primarily focus on a test of interaction between the Diet Score and 2 un-weighted Genetic Risk Scores (GRS) based on 32 SNPs for BMI (BMI-GRS) and 14 SNPs for WHR (WHR-GRS).
  - Secondary analyses will evaluate the interactions between the Diet Score and each of the SNPs in the BMI-GRS (32) and the WHR-GRS. We will use the results of step 1, above, to inform our choice of model covariates.

  ➔ **DATA SHARING TARGET FOR STEP 1: JULY 15**

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).

**Exclusions**
- Implausible dietary data (cohort-specific definition)
- Non-white race
- Missing genotype data
- Missing BMI or WHR measurements
- Prevalent diabetes (due to potential for recent dietary changes to confound this cross-sectional analysis)

**Dependent Variables**
BMI (kg/m², untransformed)
WHR (untransformed)

**Independent Variables**

**Healthy Diet Score** (identical to score proposed in ARIC ms #1738)
- ‘HEALTHY’ FOOD GROUPS (quartile ranks summed: Qt1 = 0 pts; Qt2 = 1 pt; Qt3 = 2 pts; Qt4 = 3 pts)
  - Whole Grains (defined as in our previous project)
  - Fruit (not including juice)—in all cohorts where this is feasible
  - Vegetables (not including white potatoes; not including legumes*)
  - Fish (not fried—in all cohorts where fried can be distinguished from baked, broiled, raw, etc.)
  - Nuts (including peanuts and nut butters*)

- ‘UNHEALTHY’ FOOD/BEVERAGE GROUPS (quartile ranks reversed: Qt4 = 0 pts; Qt3 = 1 pt; Qt2 = 2 pts; Qt1 = 3 pts & then summed to generate diet score)
  - Red Meat & Processed Meat (combined group*)
  - Sugar-sweetened beverages (soda pop and sugar-sweetened, artificially fruit flavored juices)
  - Fried Potatoes* (in cohorts where intake was quantified)
  - Desserts & Sweets
### Genetic Risk Factors

#### BMI associated SNPs

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### PRIMARY ANALYSES

- Interaction with **BMI-Genetic Risk Score (BMI-GRS)**: number of risk alleles summed across 32 BMI-associated SNPs reaching genome wide significance in previous GWAS for BMI (Speliotes 2010)

- Interaction with **WHR-Genetic Risk Score (WHR-GRS)**: number of risk alleles summed across 14 BMI-associated SNPs reaching genome wide significance in previous GWAS for WHR (Heid 2010)
  - Stratified by sex

### SECONDARY ANALYSES

- Interaction with each of the SNPs included in the GRS (stratified by sex when WHR is the outcome)

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**Analysis Plan: STEP 1**

### Diet Score associations with adiposity phenotypes (Primary Main "Effects" Analysis)**

**p** < 0.0083 (total, men, women) & 2 outcomes = 6 tests

**Model 1a in all participants**:

- sex**
- age (continuous)
- total energy intake (kcal intake per day, continuous)
- field center (if needed)
- principal components (or other) to account for population substructure (if needed)

**Model 1b in all participants**:

Model 1a covariates +
- other adiposity phenotype
  - BMI outcome- adjust for WHR
  - WHR outcome- adjust for BMI

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**WHR (adjusted for BMI) associated SNPs**

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**Model 2a in all participants**:  
*Model 1 covariates +*  
- education level (cohort-specific definition)  
- smoking (cohort-specific definition)  
- physical activity (cohort-specific definition)  
- alcohol intake (grams of ethanol per day, continuous)

**Model 2b in all participants**:  
*Model 2a covariates +*  
- other adiposity phenotype  
  - BMI outcome- adjust for WHR  
  - WHR outcome- adjust for BMI

**REPEAT ALL MODELS STRATIFIED BY SEX** (omit sex as covariate; run in each men and women)

**BMI-GRS and 32 individual SNP associations with BMI (Confirmatory Main “Effects” Analysis)**

*Model Covariates:*
- sex**  
- age (continuous)  
- field center (if needed)  
- principal components (or other) to account for population substructure (if needed)

**REPEAT STRATIFIED BY SEX** (omit sex as covariate; run in each men and women)

**WHR-GRS and 14 individual SNP associations with WHR (Confirmatory Main “Effects” Analysis)**

*Model Covariates:*
- sex**  
- age (continuous)  
- BMI (continuous)  
- field center (if needed)  
- principal components (or other) to account for population substructure (if needed)

**REPEAT STRATIFIED BY SEX** (omit sex as covariate; run in each men and women)

**Data Sharing**

**STEP 1: MAIN EFFECTS...**

**OF DIET SCORE ON BMI and WHR**  
*From the 4 multivariable models specified above, each cohort will provide beta regression coefficient and SE for the DIET SCORE term*

- **24 regression coefficients**—4 models for each of the 2 adiposity phenotypes in all participants (adjusted for sex) and in each men and women

**OF GRS ON BMI and WHR**  
*Each cohort will provide beta regression coefficient and SE for the GRS term, adjusting for covariates listed above*

- **6 regression coefficients**—1 model for each of the 2 adiposity phenotypes in all participants (adjusted for sex) and in each men and women

**OF 32 SNPs for BMI and 14 SNPs for WHR**  
*Each cohort will provide beta regression coefficient and SE for the SNP term, adjusting for covariates listed above*

- **148 regression coefficients**—1 model for each of the 46 adiposity-related SNPs (32 for BMI; 14 for WHR) phenotypes in all participants (adjusted for sex) and in each men and women

*An Excel file will be populated by each cohort (filename = “CHARGE DIET SCORE & adiposity traits_STEP 1_data-sharing template’)*  
*When complete, the file will be emailed to Jennifer Nettleton (jennifer.a.nettleton@uth.tmc.edu).*
TO BE COMPLETED AFTER JUNE 15
Analysis Plan: STEP 2

Diet Score x Genetic Risk Score (and individual SNP) Interaction Analysis

Model TBD (anticipated: Model 1a for BMI outcome- in all participants; Model 1b for WHR outcome- stratified by sex)

PRIMARY

Interaction between Diet Score and BMI-GRS for BMI outcome; $p < 0.05$
Interaction between Diet Score and WHR-GRS for WHR outcome in each men and women; $p < 0.025$

SECONDARY

Interaction between diet score and single SNPs (each of the SNPs included in the GRS)
32 SNPs x Diet Score for BMI; $p < 0.05/32 = 0.0016$
14 SNPs x Diet Score for WHR; $p < 0.05/(14*2) = 0.0018$ for WHR

Data Sharing

STEP 2: INTERACTIONS…
Each cohort will provide beta regression coefficient and SE for:

PRIMARY ANALYSIS: DIET SCORE*BMI-GRS product term where BMI is the outcome and DIET SCORE*WHR-GRS product term where WHR is the outcome
3 interaction regression coefficients—1 model for BMI (all participants adjusted for sex) and 1 model for WHR (adjusted for BMI) in each men and women

SECONDARY ANALYSIS: DIET SCORE*SNP product term [for each of the 32 BMI-associated SNPs and for each of the 14 WHR-associated SNPs]
46 interaction regression coefficients—1 model for each of the 32-BMI SNPs (all participants adjusted for sex) and 1 model for each of the 14-WHR associated SNPs (adjusted for BMI) in each men and women

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

Fasting glucose is the primary outcome

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

(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

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

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 website at: http://www.cscc.unc.edu/ARIC/search.php

Yes

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)?

Other from the CHARGE Nutrition working group:

1534 “Interactions between whole grain intake and genotype with respect to fasting glucose concentrations in multiple cohorts within the CHARGE & MAGIC consortia”

1577 “Interactions between zinc intake and SNPs and their impact on fasting blood glucose levels in multiple cohorts within the CHARGE and MAGIC consortia”

1675 “Low density lipoprotein receptor related protein 1, fatty acids and anthropometric traits”

1656 “Genome-wide association analysis of macronutrient intake”

1738 “Interaction between a multi-factorial diet score and genetic loci for fasting glucose and insulin”

1779 “Meta-analysis: FTO and MC4R genes, Dietary Intakes and Obesity”

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  Yes

GWAS via STAMPEDE & GENEVA, #2006.03
Interactions between Diet and Genes Related to Risk of Type II Diabetes, #2007.12

11.b. If yes—is the proposal a primarily the result of an ancillary study (numbers 2007.12 and 2006.03)

ARIC is one of 15 cohort studies contributing data to the CHARGE/MAGIC-based meta-analysis. Since this work is a product of CHARGE which utilizes GWA data, ancillaries related to STAMPEDE & GENVA are also acknowledged.

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.

The lead author is aware of, and will comply with, this stipulation.

REFERENCES


