ARIC Manuscript Proposal # 1407

PC Reviewed: 07/30/08  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

1.a. Full Title:
Interaction between FTO and dietary patterns in relation to diabetes and obesity in the Atherosclerosis Risk in Communities (ARIC) Study

1.b. Abbreviated Title:
FTO, diet, obesity and diabetes

2. Writing Group:
Writing group members: Jennifer A. Nettleton, Ellen W. Demerath, James S. Pankow, and Eric Boerwinkle

First Author: Jennifer A. Nettleton, Ph.D., Assistant Professor
Division of Epidemiology & Disease Control
University of Texas Health Science Center
1200 Herman Pressler, suite E-641
Houston, TX 77030
Phone: (713) 500-9367  Fax: 713-500-9264
Email: Jennifer.A.Nettleton@uth.tmc.edu

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

Corresponding/senior author: Jennifer A. Nettleton
Data analyst: Jennifer A. Nettleton

3. Timeline:
Data preparation and analysis will begin upon approval, and manuscript drafting will commence once suitable analytical models are finalized. Initial drafts will be circulated among writing group members within 4 months of proposal approval.

4. Background & Rationale:

Burden of Disease
Diabetes and obesity have reached epidemic proportions in the U.S. and the world, with both leading to elevated risks of cardiovascular disease and certain cancers. Exploration of the collective influence of genetic and environmental factors may help to identify strategies that reduce the burdens incurred by these conditions. The current proposal aims to address the potential interactions among dietary intake, obesity, FTO genotype and diabetes risk in the Atherosclerosis Risk and Communities study.

Diet, Adiposity, FTO genotype, and Diabetes
Complex relationships among dietary factors, obesity, FTO genotype, and diabetes risk may exist. Multiple lines of evidence independently connect each of these factors. First, measures of body weight and composition strongly influence risk of diabetes. Second, diet (quality and total intake) influence measures of adiposity as well as risk of diabetes. Third, FTO genotype
predicts measures of adiposity, and consequently, risk of diabetes\textsuperscript{1-4}. Although to date these relationships have been predominantly presented in linear fashion, the lines connecting these factors may cross, resulting in a complex tapestry weaving dietary intake, adiposity, \textit{FTO} genotype, and diabetes risk. While plausible, the collective, and perhaps interactive, influences of these factors have not been widely studied. Nevertheless, examples of analogous interactions are emerging in the literature, suggesting these interactions are not only plausible, but existent. In the context of another diabetes-risk imparting polymorphism, in the Diabetes Prevention Program investigators showed that allelic variation in the \textit{TCF7L2} gene was strongly associated with incident diabetes only in the placebo group but not in the group assigned to the lifestyle intervention (which largely involved dietary modification)\textsuperscript{5}. In the context of another important environmental factor, others have also observed interactions between physical activity and \textit{FTO} genotype with respect to body mass index\textsuperscript{6}.

**DIETARY INTAKE** \quad \Rightarrow \quad ADIPOSITY \quad \Rightarrow \quad DIABETES

\textit{FTO GENOTYPE} \quad \Rightarrow \quad \nabla

**Translating the findings of genetic studies into tangible dietary guidance**

Dietary intake can be characterized in a multitude of ways varying in complexity and number of dietary factors considered. While reductive explorations seeking to isolate an individual dietary entity, e.g., specific nutrient, are important in gathering a complete understanding of the role of diet in disease development (i.e., a focus on a tree in a dense forest), other approaches that attempt to characterize total intake or intake of multiple nutrients and food simultaneously (i.e., a focus on the dense forest itself) are valuable in terms of their potential to capture food/nutrient synergies and to provide information more readily transferable to agendas of public outreach\textsuperscript{7}.

In the current era, it is important that the findings of genetics research can be used not only in drug development, but also to improve outreach and prevention efforts. To this end, great value exists in nutrition-related research that allows for rapid translation to dietary recommendations for those with specific genotypic tendencies (“personalized medicine”\textsuperscript{8}). Thus, the current proposal will focus on the interactions between \textit{FTO} genotype and specific foods\textsuperscript{9-29} and dietary patterns\textsuperscript{30-35} (forest), as opposed to macronutrient or micronutrient intakes (trees).

We propose to study the interactions between diet and \textit{FTO} genotype with respect to measures of adiposity and risk of diabetes as well as the joint effects of these factors in ARIC.

\textit{REFERENCES ON PAGE 6}

5. **Hypotheses:**

We hypothesize the dietary intake, characterized by dietary patterns and the intakes of specific foods, will be associated with measures of adiposity and risk of incident diabetes. Further, we hypothesize that the relation between dietary intake and measures of adiposity and diabetes will depend on \textit{FTO} genotype (and vice versa).
6. Data:
Participant exclusions:
- Participants who were neither White nor African American due to small numbers
- Participants who were non-fasting (due to use of fasting glucose to determine diabetes status)
- Insufficient dietary data (extreme kcal intakes [upper and lower 1% of intake distribution, the ARIC precedent] or multiple missing responses)
- Missing FTO genotype information
- Missing measures of waist circumference or body mass index at baseline (or with no follow-up data in longitudinal analyses)
- Participants with diabetes at baseline and for whom diabetes status was unknown after the baseline exam (in longitudinal analyses only)

Outcomes:
We will conduct analyses that make use of both cross-sectional and longitudinal data.
- Cross-sectional:
  - Prevalent diabetes according to ADA criteria at baseline
  - Baseline BMI
  - Baseline waist circumference
  - HOMA-IR, fasting glucose, fasting insulin (to address potential mechanisms)
- Longitudinal
  - Incident diabetes ascertained at each of the ARIC follow-up examinations according to ADA criteria (Prevalent cases at baseline will be excluded from this analysis.)
  - Change in body weight and change in waist circumference (baseline weight – exam 4 weight)
  - Incident overweight (BMI $\geq 25$ kg/m$^2$ – prevalent overweight, BMI $\geq 25$ kg/m$^2$, will be excluded from this analysis. We will also consider analyses using alternative BMI cut-points, e.g., risk of obesity at BMI $\geq 30$ kg/m$^2$)

Exposures:
- FOOD GROUPS: To reduce the number of statistical tests, we plan to focus on three key food groups with strong history of association with diabetes and/or measures of adiposity: whole grains$^{36}$, dairy$^{16, 23, 37, 38}$, coffee$^{22, 24, 26, 27, 38}$ (expected inverse associations with diabetes and adiposity), red meat$^{28, 30, 38}$, sugar-sweetened beverages$^{25, 39}$ (expected positive associations with diabetes and adiposity).
- FOOD PATTERNS: We will also construct dietary pattern scores based on the intake of several foods as a whole to characterize their collective impact on diabetes$^{16}$ and adiposity.

For cross-sectional analyses we will utilize baseline reported diet; for longitudinal analyses we will utilize the cumulative average of dietary intake reported at baseline and exam 3, where baseline diet is used to estimate risk of outcome up to exam 3 and the average of baseline and exam 3 diet is used to estimate risk of outcome from exam 3 onward. Such an approach better reflects long-term dietary intake and helps to reduce measurement error associated with self-reported intake.

- FTO GENOTYPE: Based on previous reports, we plan to use an additive model assuming intermediate effects on outcomes within FTO heterozygotes, with strongest effects observed in risk allele homozygotes. We will use the 4 FTO SNPs typed in ARIC thus far: rs9939609, rs1421085, rs8050136, and rs17817449.
**STATISTICAL ANALYSIS:**
SAS 9.1 will be used to conduct all analyses described below separately in each ARIC Whites and African Americans.

**NOTE:** Analyses of the main effects of FTO genotype on adiposity in ARIC are in processes (Bressler, et al.). The main effects of some of the dietary factors proposed here have been demonstrated in ARIC with respect to diabetes (coffee) and metabolic syndrome (dairy, meat, sugar-sweetened beverages). Nevertheless, initial analyses will be conducted to validate our hypothesized diet-diabetes associations before stratified analyses are conducted. However, it is understood that the absence of main effects does not preclude the presence of interaction.

To minimize the number of statistical tests performed, formal tests of interaction will be conducted only where stratified analyses indicate potential differences in direction and/or magnitude of diet-outcome associations. If an interaction achieves statistical significance, results will be presented graphically or by stratified tabular comparisons. Although our approach may be modified in the process of analysis, we anticipate presenting the results as indicated in the tables below. Tertiles of dietary intake will be determined using the combined sample (not genotype specific). An alternate form of presentation where the table axes below are reversed may also be used—interaction occurs on both axes, i.e., diet modifies FTO-diabetes/obesity associations *≠* FTO genotype modifies diet-diabetes/obesity associations.

**Example Table A.** Baseline BMI according to dairy intake and FTO genotype

<table>
<thead>
<tr>
<th>FTO rs9939609 genotype</th>
<th>Dairy Tertile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tertile 1 (low intake)</td>
</tr>
<tr>
<td>TT</td>
<td>26.1</td>
</tr>
<tr>
<td>TA</td>
<td>26.5</td>
</tr>
<tr>
<td>AA</td>
<td>27.1</td>
</tr>
</tbody>
</table>

**Example Table B.** HR for diabetes according to whole grain intake and FTO genotype

<table>
<thead>
<tr>
<th>FTO rs9939609 genotype</th>
<th>Whole Grain Tertile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tertile 1 (low intake)</td>
</tr>
<tr>
<td>TT</td>
<td>1.00</td>
</tr>
<tr>
<td>TA</td>
<td>1.17</td>
</tr>
<tr>
<td>AA</td>
<td>1.21</td>
</tr>
</tbody>
</table>

**CONFOUNDERS/MODEL COVARIATES:**
*All analyses will be race stratified.*

Model 1: (minimal model) unadjusted
Model 2: adjusted for age, sex, education level, physical activity, smoking status, alcohol intake
Model 3: adjusted for variables above + total energy intake
Model 4 (for analyses where food group is an independent variable): adjusted for above + other food groups
7.a. Will the data be used for non-CVD analysis in this manuscript?  No
7.b. NA

8.a. Will the DNA data be used in this manuscript? YES, and genotyping has been completed for the FTO snp to be studied in this analysis.
8.b. 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, the author is aware of this issue.

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. There is no direct overlap between this proposal and current proposals/published manuscripts.

10. What are the most related manuscript proposals in ARIC?

In process analyses:
- ARIC (GxE-199507) 1269 Bressler. Analysis of Four Fat Mass and Obesity Associated (FTO) Gene Polymorphisms and Possible Association with Diabetes and Obesity
- ARIC-GxE (199507) 1358 Demerath. Interaction between FTO genotype and physical activity level on adiposity: The Atherosclerosis Risk in Communities (ARIC) Study

Published papers:
- ARIC 1173 Lutsey. Dietary intake and the development of the metabolic syndrome: The ARIC study.
- ARIC 930 Paynter. Coffee and Sweetened Beverage Consumption and the Risk of Type 2 Diabetes Mellitus
- ARIC 737 Stevens. Dietary fiber intake and glycemic index and incidence of diabetes in African-Americans and white adults

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use any ancillary study data? The outlined proposal is related to ARIC ancillary 2002.12 “Interactions between Diet and Genes Related to Risk of Type II Diabetes” (K01 submitted to NIDDK, funding status TBA) as well as ARIC 1995.07, Dr. Boerwinkle’s gene x environment ancillary study.
11.b. Ancillary study referenced above does not provide data in addition to that already available in ARIC. Rather it is a career award proposal based on secondary data analysis that includes ARIC among other studies involved in the CARe consortium.

12. 1-3 year completion expectation: Yes, the lead author is aware that manuscript preparation is expected to be completed in 1-3 years, and if this expectation is not met, the manuscript proposal will expire.
References


