ARIC Manuscript Proposal # 1779

PC Reviewed: 5/10/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Meta- analysis: FTO and MC4R genes, Dietary Intakes and Obesity

b. Abbreviated Title (Length 26 characters): *FTO/MC4R, Diet and Obesity*

2. Writing Group:

Writing group members:

This proposal originates from the CHARGE Nutrition Working Group and will be led by working group member **Lu Qi**, *a colleague from Harvard who is among the Nurses' Health Study and Health Professionals' Follow-up Study investigators*. Because the planned meta-analysis will comprise over 50 cohorts, each cohort is restricted to 2 authors; a 3-author exception is being granted to cohorts, like ARIC, who are providing data for 10,000+ participants. Thus, for ARIC, we propose these THREE authors to be **Jennifer Nettleton, UTHSC-H** (*CHARGE Nutrtition working group chair and ARIC analyst for this project*) **Keri Monda** and **Kari North**, UNC (*consultants and participants in data interpretation and manuscript preparation*)

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

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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).

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3. Timeline:

Data sharing by May 1, 2011; review/interpretation/ms preparation by July 1, 2001

4. Rationale:

FTO and *MC4R* are the first 2 obesity susceptibility genes with the most robust associations identified in genome-wide association studies[1, 2]. A genetic variant rs9939609 in *FTO* has been reported to be associated with energy intake[3], and we also found that the SNP rs17782313 in *MC4R* was associated with dietary fat intake[4]. However, several subsequent studies have reported inconsistent results. A meta-analysis with large sample size is needed to address this issue. In this proposal, ***we aim to examine the interrelationships between genetic variants in FTO and MC4R, dietary intakes, and BMI***.

References

1. Frayling TM. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science.* 2007;316:889-894.
2. Loos RJF, Lindgren CM, Li S, et al. Common variants near MC4R are associated with fat mass, weight and risk of obesity. *Nat Genet.* 2008;40(6):768-775.
3. Cecil JE. An obesity associated FTO gene variant and increased energy intake in children. *N. Engl. J. Med.* 2008;359:2558-2566.
4. Qi L, Kraft P, Hunter DJ, Hu FB. The common obesity variant near MC4R gene is associated with higher intakes of total energy and dietary fat, weight change and diabetes risk in women. *Human Molecular Genetics.* 2008;17(22):3502-3508.

5. Main Hypothesis/Study Questions:

In this study, we plan to test two relations:

1) The associations between FTO/MC4R variants and dietary intakes (total energy, total fat, total protein, total carbohydrate; saturated fat, polyunsaturated fat, monounsaturated fat, total fiber, glycemic load, and whole grain);

   Note: Unit of dietary factors -- total energy (kcal/day); total fat, total protein, total carbohydrate; saturated fat, polyunsaturated fat, monounsaturated fat, total fiber (g/day); whole grain (serving/day);

2) The interactions between FTO/MC4R variants and dietary intakes (described above) in relation to body mass index (BMI).

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).

STUDIES: *THIS IS A MULTI-COHORT COLLABORATION INCLUDING COHORTS INVOLVED IN THE CHARGE NUTRITION WORKING GROUP, AMONG OTHERS*

1) Studies with the genotypes of FTO rs9939609 and MC4R rs17782313 (or their proxies with r^2>0.95, which will be provided in a pre-formatted Data Collection Table); the dietary intakes (described above); and BMI.

The central analyses plan to be executed by each of the participating cohorts is shown on the following pages:

EXCLUSIONS:

1) Ethnicity: a) for studies with the majority of white participants (> 90%), please exclude non-white participants; b) for studies with the proportion of non-white participants>10%, please perform the analyses and report the data for each ethnic groups **separately**;

2) Studies of adults: please exclude participants with age < 18 y;

3) Please exclude participants (adults) with implausible total energy intakes of <500 or >4500 kcal/d;

4) Studies of children and adolescent: no exclusion

STRATIFICATION OF SAMPLE:

Analyses will be stratified as follows:

- Gender: please perform the proposed analyses in Men and Women **separately**

- Case status: if your study is case-control design, please also perform the proposed analyses in Cases and Controls **separately**

Note: If the sample contains **related** individuals, then also provide a "men+women" combined analyses and control for sex and family relatedness in all analyses.

DIETARY INTAKES:

Dietary variables include total energy, total fat, total protein, total carbohydrate; saturated fat, polyunsaturated fat, monounsaturated fat, total fiber, glycemic load, and whole grain. The dietary variables will be analyzed in two forms:

1) **Absolute intakes**: the intakes of all the dietary variables in their original unit (kcal/d, g/d, or serving/d);
2) **Relative intakes**: intakes of macronutrients (total fat, total protein, total carbohydrate; saturated fat, polyunsaturated fat, monounsaturated fat) as the percentage of total energy

Note: calculation of macronutrient intakes as the percentage of total energy

Protein% = protein [g/day] * 4)/total energy (kcal)
Fat% = fat [g/day] * 9)/total energy (kcal)
Carbohydrates% = carbohydrate [g/day] *4)/total energy (kcal)

Note: no transformation is needed. No relative intakes for total fiber, glycemic load, and whole grain.

BODY MASS INDEX

BMI= body weight (kg) / (height [m])^2
Note: no transformation is needed.

MODELS:

1) Associations between FTO/MC4R variants and dietary intakes:

MODEL 1. DIET = SNP + AGE + PHA (if available) + REGION (if available) + EVs (GWAS data only) + total energy

MODEL 2. DIET = SNP + AGE + BMI + PHA (if available) + REGION (if available) + EVs (GWAS data only) + total energy

Note: SNP is under additive model.
Note: the PHA variable is for physical activity (use usual form in each study: continuous or categorical); the REGION variable is an indicator for the participants who were enrolled from different geographic regions (e.g. states, north/central/south…) of the study; the EVs (the eigenvectors) are the p*rincipal components* analysis corrects for population stratification in GWAS.
Note: total energy is not adjusted when 'total energy' or 'Relative intakes' is the DIET variable

2) Interactions between FTO/MC4R variants and dietary intakes in relation to BMI:

Interaction test:

BMI = SNP + AGE + DIET + SNP*DIET + PHA (if available) + REGION (if available) + EVs (GWAS data only) + total energy

Note: DIET (dietary variables described above) is tested as both (1) continuous, and (2) dichotomous (HIGH INTAKE vs LOW INTAKE; defined by sex-specific median values) variable.
Note: SNP is under additive model.
Note: total energy is not adjusted when 'total energy' or 'Relative intakes' is the DIET variable

Stratified association: please run the below analysis in the LOW INTAKE and HIGH INTAKE groups defined by the sex-specific median values of DIET variables separately

BMI = SNP + AGE + PHA (if available) + REGION (if available) + EVs (GWAS data only) + total energy

Note: total energy is not adjusted when 'total energy' or 'Relative intakes' is the DIET variable

META-ANALYSIS (At Harvard School of Public Health**):**

Fixed effects meta-analysis of the ASSOCIATION or INTERACTION statistics

DATA EXCHANGE:

Please fill out the attached Data Collection tables, and send to:

Qibin Qi QIBINQI@hsph.harvard.edu
Lu Qi nhlqi@channing.harvard.edu

If you have any questions about this analysis plan, please contact us as soon as possible.

TIMELINE FOR ANALYSES:

Deadline for data sharing: May 1st 2011

FILE NAMING SCHEME

STUDY.CASE.GENDER.ETHNICITY.DATE

STUDY: study name, **<**14 characters.

CASE: If the study is a case-control study, please provide data separately for cases and controls, please use the suffix ".CASE" or ".CONTROL" after the study name.

GENDER: please provide data separately for men and women; and use the suffix 'MEN' or 'WOMEN' to indicate the file; for studies with related individuals, please also provide data for men and women together and use the suffix 'ALL' to indicate the file

ETHNICITY: please provide data separately for each ethnic groups; For the data with white participants, no suffix is needed; For the data with non-white participants, use the suffix to indicate the file.

DATE: the date on which the files are sent to us, in the format "YYYYMMDD"

EXAMPLE: NHS.CASE.WOMEN.03122011

7.a. Will the data be used for non-CVD analysis in this manuscript? 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
(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 web site at: http://www.cscc.unc.edu/ARIC/search.php

YES—no overlap

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 related projects are also from the CHARGE Nutrition working group:
1675 *"Low density lipoprotein receptor related protein 1, fatty acids and anthropometric traits"*
1656 *"Genome-wide association analysis of macronutrient intake"*
Other ARIC proposals:**

#1358; Demerath; "Interaction between FTO genotype and physical activity level on adiposity: The Atherosclerosis Risk in Communities (ARIC) Study"

#1407; Nettleton; "Interaction between FTO and dietary patterns in relation to diabetes and obesity in the Atherosclerosis Risk in Communities (ARIC) Study"

#1307; Chu; "Gene-by-Environment Interaction for Type 2 Diabetes"

***Note that leaders of the above proposals have been contacted about this proposed research and agree that there is no overlap.*

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? **__X__ Yes ____ No**

GWAS via STAMPEDE & GENEVA, #2006.03

11.b. If yes, is the proposal

_X_ 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/

(AS 2006.03)

ARIC is one of 40+ 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.

Understood, and we will meet this deadline