ARIC Manuscript Proposal 1616

1.a. Full Title: Does PPAR gamma ala12 modify the relation between dietary fat intake and measures of body composition: ARIC

b. Abbreviated Title (Length 26 characters): Diet, Gene and Obesity

2. Writing Group:
   Writing group members: Lu-Chen Weng, Lyn M. Steffen, June Stevens, Lisa Harnack, Weihong Tang

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

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3. Timeline:
   Data analysis: 3 months for analysis (Weng)
   First draft of the paper: 3 months
   Co-author review/revisions: 3-6 months

4. Rationale:
   Obesity is a major public health problem both in the US and other developed countries. In the past 20 years, the prevalence of adult obesity in many states in the US increased from less than 15 % to more than 25 % (1). Peroxisome proliferator-activated receptor gamma (PPAR gamma) belongs to the PPAR family, which is related to gene regulation of fat metabolism. The PPAR family is activated by ligand binding and, further, up-regulates, or down-regulates, gene
expression. In animal studies, PPAR gamma has been shown to regulate lipid differentiation. PPAR gamma knock-out mice died during the pregnancy period due to the shortage of body fat storage (2). In another study, PPAR gamma adipose knock-out mice showed lower body weight and total body fat even after high-fat feeding compared to control mice eating the same high-fat diet (3).

In humans, single nuclear polymorphism (SNP) on codon 12 of the PPAR gamma gene changes the amino acid product from proline to alanine (Pro12Ala), and therefore, decreases the binding ability of PPAR gamma. This means that Pro12Ala carriers have lower ability to store body fat. In children, the frequency of Ala12 carriers is greater among lean than in fat (4). However, this association was not observed in adults. In one meta-analysis of 30 independent studies, BMI was slightly higher in the Ala12 carriers than the non-carriers (5). Furthermore, Ala 12 carriers in Korean women showed a higher body weight, BMI, waist and hip ratio, and percentage of body fat than non-carriers (6). Thus, study results in children are not the same as in adults.

Fatty acids are known ligands of PPAR gamma. Few observational studies have shown differential modulation of fat intake on obesity/waist circumference among Ala12 carriers. In 2141 selected women participating in the Nurses’ Health Study, risk of obesity was positively associated with total fat intake in the non-carrier group but not in Ala12 carriers (7). In contrast, polyunsaturated fat intake was not associated with BMI in non-carriers but inversely associated with Ala12 carriers. Similar results were also observed in the Quebec Family Study of 720 healthy adults (8). Total fat intake or saturated fat intake increased waist circumference in the non-carrier group, but no association was observed between total fat or saturated fat intake and waist circumference in the Ala12 group. Recently published results from an intervention study further demonstrated the disparity of obesity control among the Ala12 carrier with high cardiovascular risk (9). After 2 years of diet intervention, Ala12 carriers consuming a Mediterranean diet including virgin oil or tree nuts, which had higher total fat, polyunsaturated fat, and monounsaturated fat content, did not change their waist circumference as much as the ala12 carriers consuming the control diet with low-fat intake. The modulation pathway on waist circumference change or change in obesity in ala12 carriers consuming different fatty acids is still unclear. In addition, previous studies have limited generalizability due to inclusion of only women or Caucasians. Cohort studies large enough to evaluate the interaction of dietary fatty acid intake, especially PUFA intake, and PPAR gamma Ala12 carrier on obesity control are needed. In addition, most studies have only examined BMI or waist circumference outcomes, but not risk of obesity. Therefore, using data from a large cohort, such as the ARIC study, we propose to evaluate the interaction of Ala12 polymorphism and fatty acid intake on BMI, waist circumference, and risk of obesity.

References

5. Main Hypothesis/Study Questions:

PPAR gamma Ala12 polymorphism carriers have a decreased ability to store fat in the body. Although the binding ability of saturated fat, monounsaturated fat, or polyunsaturated fat with PPAR gamma are different in molecular studies (10), these three types of fat may all bind to PPAR gamma. Therefore, we hypothesize that:
1) The association between dietary fat intake (regardless of the type of dietary intake of total fat, saturated fat, monounsaturated fat, or polyunsaturated fat) and change in waist circumference or BMI will be different between Ala12 carriers and non-Ala12 carriers.
2) The association between dietary intake (regardless of the type of dietary intake of total fat, saturated fat, monounsaturated fat, or polyunsaturated fat) and risk of obesity/abdominal obesity will be different between Ala12 carriers and non-Ala12 carriers.

We expect that non-ALA carriers will have a higher risk of obesity with higher dietary fat intake, and that there will not be any relation between fat intake and risk of obesity among the Ala12 carriers.

Reference
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).

1) Longitudinal study (exam 1 through exam 4):

**EXCLUSIONS:**
1) Inadequate dietary intake information or extreme energy intake
2) Participants without gene information
3) Participants with abdominal obesity or obesity at baseline for analysis examining risk of developing abdominal obesity/obesity

**EXPOSURES VARIABLES:**
- Dietary total fat intake: reported at exam 1 and exam 3 by FFQ.
- Dietary saturated fatty acid intake, polyunsaturated fatty acid (PUFA), monounsaturated fatty acid (MUFA), and total fatty acid (TFA) intake reported at exam 1, exam 3.

**OUTCOME VARIABLES:**
- Body mass index (BMI) is equal to height in meter divided by the square of body weight in kilograms.
- Waist circumference defined as girth of waist to nearest cm
- Obesity was defined as BMI $\geq 30$. (11)
- Abdominal obesity defined as waist circumference over 88 cm for women and over 102 cm for men. (12)


**MODEL COVARIATES:**
Because the frequency of polymorphism is different among each race group, we will stratify the analysis by race in each model. If the association between dietary intake and outcome are consistent among each race groups, we will combine race groups into one.
Model 1. Adjusted for age, gender, field center, and energy intake.
Model 2. Adjusted for model 1 plus physical activity, alcohol intake, and baseline smoking status.
Model 3. Adjusted for model 2 plus medication use, such as diabetic drugs (Insulin, sulphonylureas, thiazolidiones), antihypertensive drugs (Beta-blockers), anti-inflammatory drugs (Corticosteroids), anti-Psychosis (antipsychotics), and anti-depressive drugs (Tricyclic antidepressants). (13).

**STATISTICAL ANALYSIS:**
a) Using linear regression analysis, we will determine whether PPAR gamma Ala12 polymorphism modifies the relation between dietary fat intake (baseline and exam3) and body composition (exam 4) and change (exam4-baseline).
b) Using Cox proportional hazards regression analysis, we will also determine whether PPAR gamma Ala12 polymorphism modifies the relation between dietary fat intake (baseline and exam3) and the risk of obesity and abdominal obesity.

Limitations: An important limitation is the food frequency questionnaire with only 66 food items (visit 1 and 3); thus, misclassification might occur. In addition, global brand name information about foods or fat used in food preparation was collected; therefore, we were able to quantify limited types of fatty acid intake. This may result in further misclassification of fatty acid intake.

7.a. Will the data be used for non-CVD analysis in this manuscript?  __ Yes    __ 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?  __ X__ 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 ICTDER02 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  __ X _ 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.csecc.unc.edu/ARIC/search.php

___ X _ 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)?
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.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.
I am aware of this policy.