ARIC Manuscript Proposal #2593

PC Reviewed: 8/11/15  
SC Reviewed: ________  
Status: A  
Priority: 2

1.a. Full Title: Dairy Consumption and Blood Pressure: Mendelian Randomization and Gene-diet Interaction Analyses

b. Abbreviated Title (Length 26 characters): Diary, Blood Pressure, Gene, Interaction

2. Writing Group:
Lu Qi, Tao Huang(lead)
ARIC co-authors and collaborators from other cohorts are listed below.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Collaborators</th>
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<tr>
<td>ARIC</td>
<td>Shelly-Ann Love</td>
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<td></td>
<td>Misa Graff</td>
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<td></td>
<td>Kari North</td>
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<td>Gerardo Heiss</td>
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<td>NHS</td>
<td>Tao Huang, Ming Ding</td>
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<td>HPFS</td>
<td>Tao Huang, Ming Ding</td>
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<td>Women Genome Health Initiative</td>
<td>Chu, Audrey Y.,Ph.D</td>
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<td>The Cardiovascular Health Study (CHS)</td>
<td>Rozenn Lemaitre, PhD MPH</td>
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<td>The Rotterdam Study</td>
<td>M. Carola, Zillikens, Trudie Voortman</td>
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<td>The Family Heart Study</td>
<td>Mary Wojczynski</td>
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<td>the Malmö Diet and Cancer study,</td>
<td>Ulrika Ericson</td>
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<td>Young Finns Study</td>
<td>Mika Helminen</td>
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<td>Framingham</td>
<td>Mary Wojczynski, Adrienne Cupples</td>
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<td>MESA</td>
<td>Lekki Wood</td>
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<td>InCHIANTI</td>
<td>Tosh</td>
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<td>GLACIER</td>
<td>Frida Renstrom</td>
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<td>Raine Study: young birth cohort in Australia</td>
<td>Carol Wang</td>
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<td>the Danish Diet, Cancer and Health cohort</td>
<td>Tuomas Oskari Kilpeläinen</td>
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<tr>
<td>(Danish part of the EPIC study)</td>
<td>Camilla Sandholt</td>
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<td>Danish cohort called Inter99</td>
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<td>the Copenhagen City Heart Study, CCHS</td>
<td>Christina Ellervik</td>
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<td>the Copenhagen General Population Study, CGPS</td>
<td>Christina Ellervik</td>
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<td>the Danish General Suburban Population Study,</td>
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<td>DESIR: Epidemiological Study on the Insulin</td>
<td>frederic.fumeron</td>
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<td>Resistance Syndrome cohort</td>
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<td>the PREDIMED-Valencia study</td>
<td>M. Dolores Corella Piquer</td>
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<td>GOLDN</td>
<td>Smith, Caren E</td>
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<td>Health ABC</td>
<td>Denise Houston</td>
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<td>CARDIA</td>
<td>Marilyn Cornelis</td>
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Note: More coauthors will be included in this study based on contribution.
I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _TH_ [please confirm with your initials electronically or in writing]

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**3. Timeline:**  
Each cohort will complete their Mendelian randomization and gene-diet interaction analyses and provide their results to Tao Huang as soon as possible. Subsequently, an analyst from Harvard University will conduct the meta-analysis

**4. Rationale:**  
Dairy consumption has been consistently related to decreased blood pressure (1,2). However, it is not known whether this association reflects causality, since confounding from lifestyle and socioeconomic factors are difficult to fully take into account in classical observational epidemiological studies. Mendelian Randomization is a newly-developed analytical method addressing causality inference by combining genetic and epidemiological approaches (3). In order to assess the causal relation between dairy consumption and blood pressure, risk of hypertension, we plan a Mendelian Randomization analysis.


5. **Main Hypothesis/Study Questions:**
The main aim of the proposed investigation is to examine the causal effect of dairy consumption on blood pressure using an established SNP (rs4988235) as the instrumental variable.

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).**

**Study Criteria**
- Sample size: ≥500
- Follow-up time: ≥2 years (*No limitation to maximal follow-up time, please use 10 years as maximal follow-up time if there are repeated measures over time*).

**Part 1: Mendelian Randomization**
In this part, we propose to examine the effect of dairy consumption on blood pressure and risk of hypertension using SNP rs4988235 as an instrumental variable.

**Exposure, Outcome, and Instrumental Variable**
- **Outcome:** systolic blood pressure (SBP, mmHg) and prevalence of hypertension at the end of follow-up.
  - For participants who were receiving antihypertensive treatment. Please make adjustments by adding a constant value of 15 mm Hg.
  - When treating SBP as a categorical variable, please dichotomize the SBP into hypertensive (SBP ≥ 140 mmHg or use of antihypertension medication) and non-hypertensive groups, and use logistic regression model for the analysis.
- **Instrumental variable:** SNP (rs4988235)
- **Covariates:** sex, ethnicity, region, years of follow-up, as well as age, body mass index (BMI), blood pressure(mm/Hg), smoking status (current vs. former/never), physical activity, total energy intake (kcal), and alcohol consumption (all covariates at baseline).
  
  *Note: for covariate region: if the study includes several countries, or USA study includes several states, please control region.*

1) **Association between SNP and outcomes of BP/Hypertension**
   - **Systolic blood pressure (SBP)/risk of hypertension ~ SNP + study-specific covariates**
     - SNP (rs4988235): main model: CC=0, CT=1, TT=2; dominant model: CC=0, CT/TT=1; recessive model: CC/CT=0, TT=1; please treat SNP as continuous variable.
     - Study-specific covariates: baseline age, sex, ethnicity, region
     - Please check if you have made adjustments by adding a constant value of 15 mm Hg for participants who were receiving antihypertensive treatment. Please use logistic regression model when the outcome is hypertension.

2) **Association between SNP and baseline dairy intake as an outcome**
   - **Total dairy consumption ~ SNP + study-specific covariates**
     - SNP (rs4988235): main model: CC=0, CT=1, TT=2; dominant model: CC=0, CT/TT=1; recessive model: CC/CT=0, TT=1; please treat SNP as continuous variable.
     - Study-specific covariates: baseline age, sex, ethnicity, region
• Dairy consumption: continuous variable; the unit is serving/day

3) Association between diary consumption and outcomes of BP/Hypertension
Systolic blood pressure (SBP)/risk of hypertension ~ total dairy consumption + covariates
• Dairy consumption: continuous variable; the unit is serving/day
• Covariates: sex, ethnicity, region, years of follow-up, as well as age, BMI, baseline blood pressure/risk of hypertension, smoking status, physical activity, total energy intake, and alcohol consumption (all covariates at baseline).

Part 2: Gene-diet interaction
In this part, we propose to analyze the interaction of rs4988235 and dairy consumption for the outcomes of blood pressure and risk of hypertension.

Step 1. Stratified analysis on the association between diary consumption and the outcome of blood pressure by SNP (rs4988235)
Systolic blood pressure (SBP) ~ Dairy consumption + covariates
• Please split the data into three subsets by SNP rs4988235 (TT, CT, CC), and into two subsets by SNP rs4988235 (CC, TT/CT) or by SNP rs4988235 (CC/CT, TT)
• Dairy consumption: baseline; continuous variable; the unit is serving/day
• Covariates: sex, ethnicity, region, as well as age, BMI, baseline blood pressure/risk of hypertension, smoking status, physical activity, total energy intake, and alcohol consumption (all covariates at baseline).

Step 2. Stratified analysis on the association between SNP and the outcome of blood pressure by dairy consumption
Systolic blood pressure (SBP) ~ SNP + covariates
• Please split the data into three subsets based on tertiles of dairy consumption.
• SNP (rs4988235): main model: CC=0, CT=1, TT=2; dominant model: CC=0, CT/TT=1; recessive model: CC/CT=0, TT=1; please treat SNP as continuous variable.
• Covariates: baseline age, sex, ethnicity, region

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 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   ____ No
   (This file ICTDER 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 (We use the genotypic data for SNP rs4988235)

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”? ____ 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.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)?

MS 1620: Impact of Dietary Intake of Vitamins A and D on Blood Pressure and Hypertension: The ARIC Study (lead: A. Mawson)

MS 1293: Dairy intake and changes in blood pressure: the ARIC study (lead: A. Alonso)

MS 1208: Dietary intake is related to risk of developing elevated or high blood pressure in middle-aged adults: ARIC (lead: L. Steffen)

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/

12a. 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. 
In one year

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.