ARIC Manuscript Proposal #2899

PC Reviewed: 12/13/16  Status: _____  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Genetically Determined Plasma Lipid Levels and Risk of Diabetic Retinopathy: A Mendelian Randomization Study

b. Abbreviated Title (Length 26 characters): Mendelian Randomization: Lipids and DR

2. Writing Group:

Writing group members: Yong He Chong1,2*, Lucia Sobrin3*, Qiao Fan1, Alfred Gan2, Georgia Kaidonis4, Jamie E. Craig4, Jihye Kim5, Wen-Ling Liao6,7, Yu-Chuen Huang8,9, Wen-Jane Lee10, Yi-Jen Hung11, Xiuqing Guo12, Yang Hai12, Eli Ipp13, Samuela Pollack14, Heather Hancock15, Alkes Price14, Alan Pennman16, Paul Mitchell17, Gerald Liew17, Albert V. Smith18,19, Vilmundur Gudnason18, Gavin Tan2, Barbara Klein20, Jane Kuo12,21, Xiaohui Li12, Mark W. Christiansen22, Bruce M. Psaty22,23, Kevin Sandow12, Asian Genetic Epidemiology Network Consortium, Richard A. Jensen22, Ron Klein20, Mary Frances Cotch19,24, Jie Jin Wang17, Yucheng Jia12, Ching J. Chen15, Yii-Der Ida Chen12, Jerome I. Rotter12, Fuu-Jen Tsai8,25, Craig L. Hanis5, Kathryn P. Burdon26, Tien Yin Wong1,2,27**, Ching-Yu Cheng1,2,27**, I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __LS___ [please confirm with your initials electronically or in writing]

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3. Timeline: This study was initiated by Drs. Ching-Yu Cheng and Tien Y. Wong who have several Singapore-based cohorts with diabetic retinopathy data. Dr. Wong has also been an investigator of eye phenotypes in ARIC and approached us about participating in a Mendelian randomization study of lipids and diabetic retinopathy where we would perform a meta-analysis
of the data between Singapore cohorts and ARIC (as well as other cohorts). The data is already readily available because we have imputed GWAS data as part of the GWAS for diabetic retinopathy so the analyses would be completed within one month.

4. **Rationale:**
Diabetic retinopathy (DR) is a major microvascular complication of diabetes and is the leading cause of blindness in working aged adults [1]. It has been estimated that the global prevalence for any DR and proliferative DR (PDR) to be 34.6% and 7.0% respectively [2].

Dyslipidemia is a major cardiovascular risk factor, and has been suggested also as a potential risk factor for DR, in particular the more severe endpoints such as PDR and diabetic macular edema (DME) [2-4]. However, in contrast to tight glycemic and blood pressure control, which have been shown in clinical trials to reduce DR progression [5-7], therapies targeted at dyslipidemia have not shown similar results [8, 9]. In this regard, fenofibrate, a peroxisome proliferator-activated receptor alpha agonist, has shown benefits in reducing requirements for laser treatment of DR and DME [10], but the therapeutic effects of fenofibrate may not be lipid-dependent. The association of dyslipidemia with DR has been inconsistent among observational studies [11-14]. Possible reasons for this include confounding (e.g. with obesity), reverse causation and measurement biases. As such, there is difficulty in establishing a causal relationship between lipids and DR.

Mendelian Randomization (MR) is a study design utilizing genetic variants as instrumental variables (IVs) to evaluate the causal relationship between a biomarker and an outcome of interest [15]. Because it takes advantage of the natural randomization of genetic variants inherited independent of confounding factors such as lifestyle and environmental factors [16, 17], MR avoids the issues of confounders and reverse causality and serves as a practical approach to evaluate the relationship between lipids and DR.

In this study, we propose to use a MR approach pooling multiple studies to evaluate the causal relationship between lipids and two DR phenotypes: 1) any DR, and 2) severe DR by employing genetic variants associated with lipids as IVs.

5. **Main Hypothesis/Study Questions:**
To evaluate the causal relationship between lipids and DR using a Mendelian randomization (MR) approach.

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).**

We will include a total of 18 genome-wide association studies (GWAS) on DR, including African American Proliferative Diabetic Retinopathy Study (AAPDR), Age, Gene, Environment, Susceptibility - Reykjavik Study (AGES), Australian Genetics of Diabetic Retinopathy Study (AUST), Blue Mountains Eye Study (BMES), Cardiovascular Health Study-African American (CHS-AA), Cardiovascular Health Study-Whites (CHS-Whites), Genetic Center, China Medical
University Hospital, Taiwan, Genetics of Latinos Diabetic Retinopathy (GOLDR), Jackson Heart Study (JHS), Multi-Ethnic Study of Atherosclerosis-African American (MESA-AA), Multi-Ethnic Study of Atherosclerosis-Chinese (MESA-CHN), Multi-Ethnic Study of Atherosclerosis-European (MESA-EU), Multi-Ethnic Study of Atherosclerosis-Hispanic (MESA-HIS), Singapore Chinese Eye Study (SCES), Singapore Malay Eye Study (SiMES), Singapore Indian Eye Study (SINDI), Starr County Health Studies and Taiwan–US Diabetic Retinopathy Study (TUDR). Details of the individual studies have been previously described [18-33]. Of them, 17 have phenotype information on any DR and 11 on severe DR. Genotyping was performed on either the Illumina (San Diego, CA, USA) or Affymetrix (Santa Clara, CA, USA) platforms. Imputation has been done using the Markov Chain Haplotyping software IMPUTE2 or MaCH with 1000 Genomes or HapMap Phase II as reference panels.

Diabetic Retinopathy Assessment and Definition
DR has been either assessed through retinal photography or clinical diagnosis in the studies involved. DR was graded using the Early Treatment Diabetic Retinopathy Study (ETDRS) adaptation of the modified Airlie House classification system or the American Academy of Ophthalmology (AAO) International Clinical Diabetic Retinopathy Disease Severity Scale.

Two DR phenotypes will be assessed in MR analyses: 1) any DR referred to participants with evidence of presence of DR; 2) severe DR referred to participants with severe non-proliferative DR (NPDR) and/or proliferative DR (PDR) (Table 1). Controls in the GWAS analyses will be defined as type 2 diabetic patients without DR; cases will be type 2 diabetic patients with either of the defined DR phenotypes.

Genetic Instrumental Variables
We have selected lipid-associated single nucleotide polymorphisms (SNPs) at 157 loci, including 60 for high-density lipoprotein (HDL) cholesterol, 30 for low-density lipoprotein (LDL) cholesterol, 28 for triglycerides and 39 for total cholesterol, previously identified by the Global Lipids Genetic Consortium [34] in individuals of European ancestry. Summary statistics data for the association between these 157 SNPs and lipids will be used as genetic IVs for MR analyses in all ethnicities and for Caucasian cohorts. We will then test the effects of these 157 SNPs on plasma lipid levels in East Asian populations from the Asian Genetic Epidemiology Network (AGEN) consortium, identified 51 SNPs (28 for HDL cholesterol, 10 for LDL cholesterol and 13 for triglycerides) associated with lipids (P < 0.05) in East Asians and used them for MR analysis in Chinese groups.

Statistical Analysis
We will obtain GWAS summary statistics data from individual studies for either or both DR phenotypes for the SNPs where genotype and imputed data are available. We will then perform inverse variance-weighted, fixed-effect meta-analyses with METAL software to pool available GWAS summary data for each SNP for both DR phenotypes from individual studies. Individual SNP data will be pooled from all studies, as well as studies from Caucasian and Chinese cohorts separately.

Next, the association between lipids and DR at each SNP will be calculated as \( \beta_{\text{lipid-DR}} = \beta_{\text{SNP-lipid}} / \beta_{\text{SNP-DR}} \) [35] where \( \beta_{\text{lipid-DR}} \) represents the estimated effect size (logarithm of the odds ratio...
[OR]) of 1 standard deviation (SD) increase in genetically determined plasma lipid levels on DR. To assess the association between each lipid trait and DR, we will combine the $\beta_{(lipid-DR)}$ estimates across multiple SNPs using fixed-effect meta-analysis.

We will perform the same analysis for 2 subgroups of studies for each DR phenotype where the IVs were presumed to be stronger on account of similar ancestry backgrounds: 1) among studies of Caucasian ancestry using the 157 SNPs identified by the Global Lipids Genetic Consortium as IVs, and 2) among studies of Chinese ancestry using 51 SNPs from the AGEN consortium as IVs. All statistical analyses will be performed using Stata 14 (StataCorp LP, College Station, TX).

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

Admixture Genetic Mapping for Diabetic Retinopathy Genes in African Americans (already published)

A genome-wide association study for severe diabetic retinopathy in Scotland (recently submitted)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _X___ Yes    ____ No
11.b. If yes, is the proposal
   _X__  A. primarily the result of an ancillary study (list number* 2011.08_)
   ___  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.csc.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.

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.csc.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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes _X___ No.

References:


