ARIC Manuscript Proposal #3413

PC Reviewed: 6/18/19	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Genetic susceptibility and lifetime risk of type 2 diabetes

b. Abbreviated Title (Length 26 characters): Genetics & T2D lifetime risk

2. Writing Group:
Symen Ligthart, Natalie Hasbani, James Pankow, Elizabeth Selvin, Eric Boerwinkle, Alanna Morrison, Paul de Vries, Abbas Dehghan

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **__SL___ [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: Analyses have already been done in the Rotterdam Study, and a draft manuscript based on those results has already been written. So as not to delay the project, we are proposing an aggressive timeline for the analyses in ARIC. We expect analyses to be done 2-3 weeks after approval of the manuscript proposal and expect to a draft manuscript to ready 4-6 weeks after approval of the manuscript proposal.

4. Rationale: In a 2016 paper (PMID: 26575606), Dr. Ligthart examined the lifetime risk of developing impaired glucose metabolism in the Rotterdam Study, a prospective, population-based cohort study from the Netherlands. The current manuscript proposal hopes to expand on these findings by looking at how genetic susceptibility affects lifetime risk, in both the Rotterdam Study and the ARIC study.

5. Main Hypothesis/Study Questions: The main study question is how the lifetime risk of type 2 diabetes differs among individuals with low, intermediate, and high genetic susceptibility, as determined by multi-SNP genetic risk scores. We hypothesize that there will be differences, with higher genetic susceptibility corresponding to higher lifetime risk.

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).

Analyses will be performed separately for the Rotterdam Study and the ARIC study without meta-analysis. All ARIC analyses will be performed by ARIC investigator Dr. de Vries and his colleagues at the University of Texas Health Science Center at Houston. All Rotterdam Study analyses will be performed by Dr. Ligthart and his colleagues at the Erasmus University Medical Center.

Analyses in ARIC will be restricted to European ancestry participants because the genome-wide association studies used to create the genetic risk scores included mainly individuals of European ancestry, so genetic risk prediction in other ancestry groups is currently not optimized. The analysis will also be restricted to participants free of type 2 diabetes at baseline (visit 1), since we will be analyzing incident type 2 diabetes events as the outcome. This will be done by including only participants with diabts03 = 0. Incident diabetes is captured using a combination of diagnosis, medication and glucose data captured at visits 1 through 6, supplemented with annual follow-up self-report data after visit 4 to account for the longer time between visits (PMID: 20200384).

Genetic risk scores will be created for ARIC participants based on their genotype dosages for a selection of genetic variants that were genome-wide significant in the largest available genome-wide association study of type 2 diabetes (PMID: 30297969). Beta coefficients (corresponding to the per-allele effect size on type 2 diabetes) of the included genetic variants will be used to weigh the contribution of each genetic variant to the genetic risk score. Participants in the lowest quintile (<25%) of the genetic risk score will be considered to have low genetic susceptibility, while participants in the highest quintile (>75%) of the genetic risk score will be considered to have high genetic susceptibility. All other participants will be considered to have intermediate genetic susceptibility.

Remaining lifetime risks at different ages were calculated for type 2 diabetes using a modified version of survival analysis, accounting for the competing risk of death. The absolute remaining lifetime risk is calculated using incidence rates, hazard ratios, and mortality rates. Dr. Ligthart and his colleagues have previously applied this method to the Rotterdam Study to estimate the lifetime risk of type 2 diabetes (PMID: 26575606) and to examine sex differences in the lifetime risk of cardiovascular disease (PMID: 25403476). We will calculate the remaining lifetime risks at index ages 45, 55, 65, and 75 years, stratified for genetic risk category (low, intermediate, and high). Important covariates for type 2 diabetes such as age, sex, and BMI will also be considered in the analysis.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __x__ No

Type 2 diabetes is an important CVD risk factor.

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

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/mantrack/maintain/search/dtSearch.html

___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)?

#1273, with corresponding author Dr. James Pankow. Dr. Pankow has been included in the current proposal.

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* ___2006.03_____)
___ 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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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.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.