ARIC Manuscript Proposal # 3616

PC Reviewed: 5/12/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Relationship between polygenic risk score and Life's Simple 7 guidelines on the lifetime risk of coronary artery disease.

b. Abbreviated Title (Length 26 characters):

2. Writing Group: Natalie R. Hasbani, Alanna C. Morrison, Eric Boerwinkle and Paul S. de Vries

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **NH**

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3. Timeline: We expect analyses to be done 3 months after approval of the manuscript proposal and expect to a draft manuscript to be ready 6 months after approval of the manuscript proposal.

4. Rationale: Polygenic risk scores for coronary heart disease are being widely considered as a clinical screening tool to guide early intervention for coronary heart disease (CHD). However, the extent to which polygenic risk scores are modified by the current lifestyle guidelines from the American Heart Association (AHA) has not been well established, especially as they relate to remaining lifetime risk. In addition, current publications typically describe the risk of CHD over shortened follow-up times (i.e. 5-year or 10-year risk) and are unable to compute remaining lifetime risk for CHD, accounting for the important competing risk of death.

5.Main Hypothesis/Study Questions:
The aim is to quantify how the lifetime risk of CHD differs according to polygenic risk and Life's Simple 7 guidelines.

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).

This is a survival analysis of the ARIC prospective cohort study evaluating the effect of a polygenic risk score (PRS) and the AHA's Life's Simple 7 on predicting incident CHD.

Primary analyses will be restricted to European ancestry participants since the genome-wide association studies used to create the polygenic risk scores included mainly individuals of European ancestry. We will then replicate these analyses in the African American population, noting this important limitation. Both analyses will be restricted to participants free of cardiovascular disease (prvchd05=1) since we will be analyzing incident cardiovascular events as the outcome. Individuals on statins (statincode01=1) or missing risk factors used to compute Life's Simple 7 at visit 1 will also be excluded.

A PRS based on over six million genetic variants was previously developed using LDPred (Khera et al; PMID: 30104762). PRS scores will be computed among ARIC participants using the per-allele weights provided by Khera et al. The score will be analyzed both as a continuous and categorical variable. Participants who scored in the lowest 20^{th} percentile will be considered to have low genetic susceptibility, while participants who scored in the top 20^{th} percentile will be considered to have high genetic susceptibility. All other participants will be considered to have intermediate genetic susceptibility.

Life's Simple 7 score ranges from 0 to 7 and is computed by counting the number if ideal health factors individuals score in 7 areas of cardiovascular risk, including smoking status, body mass index, cholesterol, blood pressure, blood glucose, diet and physical activity according to the AHA recommendations. Life's Simple 7 will be calculated using data obtained visit 1, Healthy diet information will come from the administered food frequency questionnaire and derived nutrition variables. As Life's Simple 7 score has been previously calculated for the ARIC cohort, we will confirm our scoring metric mirrors previously published work for consistency and validation.

Cox proportional hazard regression will be utilized to evaluate the relationship between the PRS, Life's simple 7 and incident CHD. Remaining lifetime risks at different ages will be calculated for CHD using a modified version of survival analysis, accounting the competing risk of death. 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). Using the full cohort at age 45, remaining lifetime risk calculated according to Life's Simple 7 score and genetic risk category.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _X_ 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

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)?

Among the proposal from the last few years, #2742 is the most related. Our writing team partially overlaps with theirs (Alanna Morrison, Paul de Vries). The biggest differences between the proposals are that #2742 focuses on atherosclerotic cardiovascular disease (ASCVD) as an outcome instead of CHD, and that #2742 aims to describe differences between the performance of a genetic risk score between European and African Americans, whereas the current proposal is focused on European Americans. This proposal will also focus on the potential interaction of genetic risk scores with Life's Simple 7 guidelines and will report the remaining lifetime risk rather than 10-year risk of CHD.

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
___ 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.