ARIC Manuscript Proposal #3677 (revised)

PC Reviewed: 9/8/20 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: An Evaluation of Life's Simple 7 Score in Midlife in Offsetting the Genetic Risk of Dementia

b. Abbreviated Title (Length 26 characters): Midlife health, gene, dementia

2. Writing Group:

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

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3. Timeline: Analysis will start immediately after aricpub approval with a draft manuscript for circulation in 9 months if only ARIC data are used. If other cohorts participates, the time will be longer.

4. Rationale:

Among older adults (aged ≥ 65) in the U.S., ~8% live with dementia.[1] Available pharmacologic treatment options are limited and have small benefits.[2] Non-pharmacologic intervention, such as

physical activity, is recognized as possible prevention and management options.[3] A healthy lifestyle has been shown to offset the genetic risk of dementia among white participants aged ≥ 60 in the large cohort of UK Biobank (UKB) with eight years of follow-up.[4] Among those in the top quintile of dementia genetic risk, a favorable lifestyle reduced the risk of dementia by 32%.[4] However, in the Rotterdam study, with a median follow-up of 14 years, a favorable lifestyle was significantly associated with lower risk of dementia only among those with low or intermediate genetic risk and not among those with high genetic risk.[5] In the UKB study, all-cause dementia status was based on the International Classification of Diseases (ICD) codes in hospital inpatient records or death register data. In the Rotterdam study, dementia ascertainment included the use of in-person and informant interview and electronic health record data with the final diagnosis decided by a consensus panel led by a consultant neurologist according to the standard criteria for dementia in DSM-III-R. In both the UKB and Rotterdam studies, the genetic risk of dementia was estimated based on results from large-scale genome-wide association studies (GWAS) of Alzheimer's disease (AD), the most common form of dementia. The diverged findings from the UKB and the Rotterdam studies suggest the need for more research on the interplay between genetic risk and lifestyle to generate evidence on using lifestyle modification for the prevention and treatment of dementia.

To this end, several aspects in this research area need to be extended. First, the UKB and the Rotterdam studies included only white participants. African Americans have over 30% higher risk for dementia compared with whites in the U.S.[6] The extent that a healthy lifestyle could offset genetic risk of dementia in African Americans has not been assessed. Further the genetic burden of AD in African Americans may differ from populations of European ancestry.[7] Second, the health factors in the UKB study included smoking, physical activity, diet, and moderate alcohol consumption and those in the Rotterdam study included smoking, depression, diabetes, physical activity, social isolation, and diet. Having protective vascular factors, including maintaining BMI, total cholesterol, blood pressure, and fast glucose in the healthy range have been associated with lower risk of dementia, cognitive decline, or levels of markers of neurodegeneration in both European and African Americans.[8-16] These vascular factors are highly influenced by diet and physical activity. The Life's Simple 7 (LS7) score summarizes seven lifestyle and vascular factors for defining cardiovascular health (no current smoking, engaging in moderate to intense physical activity, having a healthy diet, and maintaining BMI, total cholesterol, blood pressure, and fasting glucose in the healthy ranges). The LS7 score, ranged from 0 to 14, has been categorized into poor (0-8), intermediate (9-10), and ideal (11-14).[17] Ideal LS7 scores have been associated with lower risk of dementia in the Multi-Ethnic Study of Atherosclerosis (MESA) with approximately 10 years of follow-up. In the Whitehall II cohort with approximately 25 years of follow-up, optimal LS7 scores (12-14) have been associated with lower risk of dementia compared to the intermediate (7-11) and the poor (0-6) categories.[18,19] In the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, the highest tertile of an adapted LS7 score has been associated with lower risk of incident cognitive impairment.[20] The LS7 score may be more informative than lifestyle factors on the effects of physical health in offsetting genetic risk of dementia. Finally, the UKB study only has about 8 years of follow-up. Neurodegeneration can start over 10 years before the appearance of symptoms for Alzheimer's disease.[21] A study with longer follow-up can inform the need for early intervention.

We propose to study the extent that higher LS7 score in midlife would offset the genetic risk of dementia using both white and black populations. Given that the APOE4 variant accounts for ~80% of the known genetic risk for AD in populations of European ancestry,[22] we will also conduct a focused study on the extent that higher LS7 score in midlife would offset the risk of dementia among individuals with different APOE4 variants.

The initial analysis will be conducted in ARIC, then we will invite other cohorts to participate. Cohorts with non-white participants having relevant data (genetics, LS7, and incident dementia) are: MESA, CHS, …

5. Main Hypothesis/Study Questions:

Primary hypothesis. Higher LS7 score will substantially offset the genetic risk of dementia estimated using the results of GWAS of AD in both race groups.

Secondary hypothesis. Higher LS7 score will substantially offset the risk of dementia due to the APOE4 risk variants in both race groups.

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 design: longitudinal cohort study with ARIC visit 1 as the baseline

Inclusion criteria: Participants with self-reported race as white from Minnesota, Forysth, Washington county and black from Jackson and Forysth and with data in the exposure, outcome, and covariates.

Exposure: Dementia polygenetic risk score (PRS) based on GWAS results of AD and LS7 scores.

Outcome: Incident dementia up to the end of visit 7 (December 31st, 2019) using the level 3 definition published previously.[8] This definition included the use of cognitive tests from visits 2 and 4, adjudicated dementia from complete evaluation at the ARIC-NCS visit (visit 5), dementia classified based on Telephone Interview for Cognitive Status–Modified (TICSm), dementia based on informant telephone interviews using a modified version of the Clinical Dementia Rating and the Functional Activities Questionnaire among a subset identified as having suspect dementia, or dementia cases identified solely by surveillance based on a prior discharge hospitalization ICD-9 or death certificate code for dementia.[8]

Other variables.
Demographics and genetics: age, sex, race, center, education levels, prevalent coronary heart disease, genetic principal components for controlling for subpopulation stratification.

Data analysis:

Modeling of the exposure variables (PRS and LS7). Our current goal is to use these exposure variables as three-category variables for comparisons with other studies.[4,23] When the categories are used as the main effect, the average effects of one category vs the others are estimated. When the categories are used for stratifying the cohort for analysis, the effects of the predictors within a category are estimated. This categorical approach does not require distribution assumptions. We will evaluate whether published cut points are acceptable for our data instead of trying to optimizing the cut points within our data, which may lead to the loss of generalizability.[24] Categorization may fit better into clinical decision making but can incur cost in statistical analysis, such as the reduction of power.[24] Therefore, we will also analyze these two exposures as continuous variables. The presentation of the results of the categorical or the continuous analysis or both in the manuscript will be decided after reviewing the results.

Derivation of the PRS for dementia: We will use the approach similar to the UKB study where summary statistics of large-scale GWAS of AD were combined with individual-level genetic data to derive the PRS for dementia using the score command in PLINK.[4,25] To estimate individual genetic risk for dementia requires reliable results from large-scale genetic association studies. Given the lack of large-scale published GWAS of all-cause dementia (one is ongoing in CHARGE) and the availability of large-scale GWAS of AD,[26,27] the most common form of dementia,[28] estimating the genetic risk for dementia using summary statistics of GWAS of AD is an acceptable approach. In addition, patients with clinical AD often present with other dementia pathologies.[29,30] GWAS summary statistics of AD could have captured genetic risk for other forms of dementia.

The AD GWAS summary statistics for whites will be from Kunkle et al. 2019 and those for blacks will be from Reitz et al. 2013.[26,27] Given that AD is the most common form of dementia, accounting for 50% to 80% of the dementia cases in the U.S. and European countries[31-34], and both of these GWAS results of AD had rigorous ascertainment of cases and controls, these GWAS results represent the best approximation to the genetic risk of dementia to date. To summarize, in the Kunkle et al. study, 46 case-control studies with a total of 21,982 cases and 41,944 controls participated in the discovery stage. The cases were clinically confirmed to have AD. Among the controls, 83% were determined to be cognitive normal at age > 60, and most were clinical confirmed as cognitively normal with the exception of the 1958 British Birth Cohort (n=5342).[26] In the Reitz et al. study, cases were classified according to National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria.[35] The genetic data of the ARIC participants will be imputed using the TOPMed reference panel.[36] We will submit an application to NIAGADS to obtain the summary statistics from Reitz et al., and those from Kunkle et al. are publicly available. The genetic variants from the GWAS summary statistics will be first clumped using an r2 threshold of 0.2 and a window of 1 Mb. We will evaluate the applicability of the p-value threshold of 0.5 for calculating the PRS used in the UKB paper in ARIC.[37]

Modeling of PRS for dementia. PRS have been categorized into 3 groups: low (quintile 1), intermediate (quintiles 2 to 4), and high (quintile 5) in studies similar to the present study.[4,23] We will evaluate whether these cut points are appropriate for our data, for example, whether the

number of cases in each strata fit the rule of thumb for the minimal number of cases.[38] In categorical analyses, the cut points will be derived within each race group. We will investigate whether it is appropriate to derive the cut points in the race-combined cohort.

Derivation of LS7 scores. The LS7 scores will be calculated using the methods reported previously based on the recommendation from the American Heart Association,[39,40] where each of the LS7 metrics is coded in three categories (poor=0, intermediate=1, and ideal=2), then these scores are summed into an overall LS7 score ranged from 0 to 14.

Modeling of LS7 scores. We will evaluate appropriate cut points for categorizing the LS7 score into 3 groups (low, intermediate, and high) based on previous reported cut points[17,19] and using an approach as described above for categorizing PRS.

Primary analysis using PRS and LS7 as categorical variables

Survival analysis. Given the long follow-up time, we will use competing risk survival analysis based on the Fine & Gray method to account for mortality, which can preclude the development of dementia.[41] We will plot the cumulative incidence curves without assuming non-informative censering.[42] We will also use Cox regression to estimate the cause-specific hazard ratios for comparison. Significance level will be set at p-value < 0.05.

Race-stratified analysis. Given genetic risk for dementia may differ by race, we will conduct survival analysis stratified by self-reported race. The methods for meta-analysis to combine the results from the race groups, e.g. fixed or random effects, will depend on the results from the assessment of heterogeneity.[43]

Race-stratified models. Models will be used to assess (1) the main effects of PRS and LS7, (2) effect modification between PRS and LS7, and (3) the effects of PRS and LS7 within the strata of the other.

The null model (M0) will include the covariates: age, sex, center, education levels, prevalent coronary heart disease, and genetic principal components.

1) Main effect models:
   1.a. Genetic risk main effect model. M1a: M0 + PRS groups
   1.b. LS7 main effect model. M1b: M0 + LS7 groups

2) Effect modification model: M2: M0 + PRS groups + LS7 groups + PRS groups x LS7 groups. The interaction term will be used to evaluate effect modification between PRS and LS7

3) PRS and LS7 stratified models:
   3.a. For each genetic risk group. M3a: M0 + LS7 groups, for assessing the effects of LS7 within each of the three PRS groups.
   3.b. For each LS7 group. M3b: M0 + PRS groups, for assessing the effects of PRS within each of the three LS7 groups.

Secondary analysis using PRS and LS7 as continuous variables

Similar to the primary analysis, both competing risk and Cox regression analyses will be conducted. We will obtain effect estimates using the main effect and effect modification models (#1 and #2 in the primary analysis). No stratified models are necessary. If the PRS and LS7 interaction term is not statistically significant, the extent that each unit of LS7 offsetting the genetic risk will be assumed to be constant across the full range of the values.

Secondary analysis using APOE genotypes and LS7 as exposures

The analysis will be similar to the primary analysis, except that the genetic risk variable will be stratified by APOE haplotypes. We will consider the 6 haplotypes of APOE (e2/e2, e2/e3, e2/e4, e3/e3, e3/e4, e4/e4) since the risk association of each haplotype for AD differ.[44] If the number of individuals in some haplotypes is too small for analysis, we will consider grouping some haplotypes together. For example, grouping one copy of e4 and two copies of e4 together. The most common haplotype, e3/e3, will be the reference group.[44]

Limitations:

1) The proposal only includes white and black populations because the lack of large-scale genetic association studies of AD or dementia in other populations, e.g. Hispanics. We will include more race groups as summary statistics of large-scale GWAS of dementia in other populations are available.
2) The difference in genetic risk for AD by sex may affect the interplay between dementia genetic risk and health factors.[45] To estimate the genetic risk for dementia by sex would require sex-stratified genetic association studies of AD or dementia, which still have limited sample size to date.[46]
3) Comparison between the UKB study and the present study on the dementia risk estimates due to genetics and health factors would be difficult due to different eras and countries even if we use the same health factors as in the UKB study.
4) The analysis using APOE haplotype will not be able to capture known modifying genetic risk factors of APOE.[47]
5) We plan to use GWAS results of AD to develop a PRS while the outcome of this proposal is dementia. Therefore, a gap exists between the phenotype of the GWAS and the outcome of the current study. As explained in the data analysis section, the GWAS results of AD are the best approximation to the genetics of dementia available to date largely due to the rigorous case and control definitions of the participating studies and AD being the most common form of dementia. Better alternatives do not seem to exist until the large-scale GWAS of dementia in CHARGE reach fruition. For example, the UKB is a publicly available database and has a large sample size. However, its ascertainment of dementia is based on ICD code, which have been shown to have low to moderate sensitivity for capturing dementia (32% for ICD-9 and 67% for ICD-10).[48] So a PRS of dementia based on the UKB dementia ascertainment would likely miss a substantial portion of the genetic signals.
6) Given that PRS will be generated using the results of the GWAS of AD, the effect of LS7 on dementia risk within the PRS strata may be specific to the AD form of dementia. The

overall direction is to use the best approximation of the genetics of dementia to generate PRS and study the relation between the PRS and lifestyle and clinical factors.

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

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)?

1898 Midlife cardiovascular health and 20-year cognitive decline: Atherosclerosis Risk in Communities Study results
2383 The Relationship of Midlife Cardiovascular Health with Late Life Physical Performance: the Atherosclerosis Risk in Communities Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X_ Yes ____ No

ARIC NCS

11.b. If yes, is the proposal
_X_ A. primarily the result of an ancillary study (list number* _ARIC Hemostatic factor and NCS ancillary studies**____)**
___ 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.

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.

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 ____ No.

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