ARIC Manuscript Proposal #3849

PC Reviewed: 5/11/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Racial and Ethnic Differences in the Population Burden of Dementia Attributable to Modifiable Risk Factors among Americans

b. Abbreviated Title (Length 26 characters): **Dementia PAFs by Race**

2. Writing Group:

Writing group members: Mark Lee, Christy Avery, Tom Mosley, Michael Griswold, Rebecca Gottesman, Timothy Hughes, Sanaz Sedaghat, Gerardo Heiss, Pamela L. Lutsey

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

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3. Timeline:

Data analysis will begin after approval.

4. Rationale:

As the American population ages, the number of people affected by dementia is projected to rise markedly in coming decades—from approximately 5.8 million in 2020 to 13.8 million by 2050.[1]

Correspondingly, the annual costs associated with dementia care are expected to rise from $290 billion to $1.1 trillion over the same time frame.[2] In response to this looming epidemic, the federal U.S. government has set an ambitious goal to prevent and effectively treat dementia by 2025.[3] Because no cure for dementia currently exists, prevention efforts targeting modifiable dementia risk factors are important.

The burden of dementia may be most acutely felt among Americans who are members of racial and ethnic minority groups. Compared with prevalence among non-Hispanic White Americans, the prevalence of dementia is twice as high among Black Americans and 1.5 times as high among Hispanic Americans.[4] To reduce disease disparities, it is important to consider whether prevention efforts will be equally effective across racial and ethnic groups.

A report by the *Lancet* Commission identified 12 potentially modifiable factors with strong evidence of being causally related to incident dementia risk: low education, hearing loss, traumatic brain injury, excessive alcohol consumption, hypertension, obesity, smoking, depression, social isolation, physical inactivity, diabetes, and air pollution.[5] The timing of these risk factors across the life course varies. The authors of the Lancet report categorized the risk factors as occurring during early life (education), midlife (hearing loss, TBI, hypertension, excessive alcohol consumption, obesity), or later life (smoking, depression, social isolation, physical inactivity, diabetes, air pollution). Using risk ratios derived from meta-analyses and global prevalence data, the authors calculated that 40% of dementia cases worldwide could be attributed to these risk factors.

Previous research has examined how the burden of dementia attributable to these risk factors varies across populations.[6,7] In low- and middle-income countries, the proportion of dementia cases attributable to this group of risk factors tends to be higher: 40% in China, 41% in India, and 56% in Latin America.[8] This is because the prevalence of these risk factors varies substantially across these populations. These differences signal the power of social and public health policies in shaping dementia rates.

To date, no research has investigated differences in the burden of dementia attributable to modifiable risk factors within sub-groups of a single population. In the United States, there are dramatic racial and ethnic inequalities in the prevalence of many of these risk factors. For instance, the percent of Americans 25 and older without a high school diploma is 7.4% among non-Hispanic Whites, 14.5% among non-Hispanic Blacks, 32.4% among Hispanics, and 13.1% among Asians. Because of this, the contribution of any given factor to dementia rates may differ substantially between racial and ethnic groups in the U.S. Estimating these differences can help identify interventions to reduce dementia rates *and* minimize racial disparities.

The goal of this study is to estimate the percentage of dementia cases among non-Hispanic White, non-Hispanic Black, Hispanic, and Asian Americans attributable to low education, hearing loss, traumatic brain injury, excessive alcohol consumption, hypertension, obesity, smoking, depression, social isolation, physical inactivity, diabetes, and air pollution. We will also calculate the proportion of dementia cases for each race that could be prevented from a 5% proportional reduction in the prevalence of each risk factor. Additionally, we will calculate the

preventable number of dementia cases per 100,000 person years with a 5% proportional reduction in the risk factor.

To calculate PAFs, we will use risk ratios from the most recent meta-analyses along with race-specific prevalence estimates from nationally representative data (e.g., NHANES). Because many of the risk factors co-occur within individuals, we will adjust PAF estimates for communality to calculate the proportion of dementia cases attributable to all risk factors combined. To do this, we will conduct factor analyses using ARIC data, in which all risk factors have been measured. Methods for doing this have previously been described.[9]

5. Main Hypothesis/Study Questions:

Study questions: What are the PAFs among Blacks, Whites, Hispanics, and Asians attributable to low education, hearing loss, traumatic brain injury, excessive alcohol consumption, hypertension, obesity, smoking, depression, social isolation, physical inactivity, diabetes, and air pollution?

Hypotheses: The proportion of dementia cases attributable to potentially modifiable risk factors will be greater among Black and Hispanic Americans than it is among White and Asian Americans.

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: To calculate PAFs, we will use risk ratios from most recent meta-analyses (reported by the Lance Commission[5]) combined with race-specific prevalence estimates of each risk factor based on nationally representative data (e.g., NHANES). We will weight each risk factor's PAF based on communality (using ARIC data) to calculate the fraction of dementia cases attributable to all risk factors combined.

Inclusion/Exclusion: To calculate communality weights, we will exclude ARIC participants with missing data on the relevant risk factors (see below).

Risk Factors Measured in ARIC:

- Low education (<high school)
- Hearing loss (≥25 decibels hearing level based on audiometric examination)
- Hypertension (defined by blood pressure and/or medication)
- Excessive alcohol consumption (8+ drinks/week for women, 15+ drinks/week for men)
- Obesity (BMI ≥30 kg/m^2)
- Smoking
- Depressive symptoms (CES-D score ≥9)
- Physical inactivity (not meeting guidelines of 75 min/week of vigorous or 150 min/week of moderate activity)
- Diabetes (defined by fasting glucose, A1c, and/or medication)
- Social isolation (living alone according to household roster)

- TBI (from V5 neurological history form)
- Air pollution (ambient air quality in participant's neighborhood)

Statistical analysis:

First, to calculate the unweighted PAFs for each risk factor, we will use the standard formula $P_{e,r}(RR_e-1)/(1+P_{e,r}[RR_e-1])$ in which $P_{e,r}$ is the prevalence of exposure *e* for race group *r* and RR_e is the relative risk of dementia associated with that exposure.

Next, using ARIC data, we will calculate the communality weights for each risk factor. To do this, we will conduct a principal component analysis to identify latent variables that explain the variance in the observed risk factors. Weights for each risk factor will be calculated as one minus the sum of the square of all factor loadings (i.e., how much each unobserved component explained each measured variable). Then, we will use these weights to calculate the adjusted proportion of dementia cases for each race group attributable to all risk factors combined. We will use the formula $PAF_{combined} = 1-[(1-w*PAF_1)(1-w*PAF_2)(1-w*PAF_3)\ldots]$ where PAF_1 is the unweighted PAF for the first risk factor, and so on. This method is adopted from the Lancet Commission report.[5]

Next, to evaluate the impact of a proportional 5% reduction in risk factor prevalence, we will calculate potential impact factors (PIFs) using the formula $PIF = \frac{\sum_{i=1}^{n} p_i\, RR_i - \sum_{i=1}^{n} p'_i\, RR_i}{\sum_{i=1}^{n} p'_i\, RR_i}$ where p_i is the observed proportion of cases at the *i*th exposure level and p'_i is the counterfactual proportion of cases at that level given a 5% reduction. We will use the results of the PIF calculation to estimate how many cases of dementia per 100,000 could be prevented with a 5% reduction in risk factor prevalence for each race group.

Limitations:

This analysis has several notable limitations. First, the risk ratios used in our PAF calculations are drawn from meta-analyses in which the exposure variable was not operationalized and measured in a uniform way. There will also likely be some differences in how the exposure was operationalized and measured for estimating the RR and how it was operationalized and measured in national prevalence estimates. Additionally, absent reliable evidence to the contrary, we will assume that the relative risk of dementia associated with each risk factor does not vary across racial and ethnic groups. For some risk factors (e.g., TBI), it may be difficult to get race-specific prevalence estimates. In this case, we will either drop these risk factors from our analysis or include them only for groups with available data. Our interpretation of the measures of impact will be cautious, acknowledging the general assumptions of measures of impact (e.g., the exposure is causal).[10]

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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? ____ Yes __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ 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)?

#3677 – An evaluation of Life's Simple 7 score in midlife in offsetting the genetic risk of dementia

#3581 – The moderating influence of education and lifestyle on genetic risk for dementia

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* 2008.06)
___ 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 https://sites.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.

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