ARIC Manuscript Proposal #3946

PC Reviewed: 10/12/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Developing Simple Regression Models to Enhance a Simulation to Explore the Effects of Life-Course Blood Pressure Treatment on Racial Disparities in Cardiovascular Events and Cognition

b. Abbreviated Title (Length 26 characters): BP COG Simulation Methods Paper

2. Writing Group:

- Steve Sidney, MD, MPH, Kaiser Permanente, Oakland, CA, USA steve.sidney@kp.org;
- Rod Hayward, MD, University of Michigan, Ann Arbor, MI, USA, rhayward@umich.edu
- Andrzej Galecki, PhD, MD, MS, University of Michigan, Ann Arbor, MI, USA, agalecki@umich.edu
- Bruno Giordani, PhD, University of Michigan, Ann Arbor, MI, USA, giordani@med.umich.edu
- Emily Briceño, PhD, University of Michigan, Ann Arbor, MI, USA, emilande@med.umich.edu
- Rachael Whitney, PhD, University of Michigan, Ann Arbor, MI, USA, whitnera@med.umich.edu
- Jeremy Sussman, MD, MS, MS, University of Michigan, Ann Arbor, MI, USA, jeremysu@umich.edu
- Rebecca Gottesman, MD, PhD, Johns Hopkins University, Baltimore, MD, USA, Rebecca.gottesman@nih.gov
- Alden Gross, PhD, Johns Hopkins University, Baltimore, MD, USA, agross14@jhu.edu
- Darrell Gaskin, PhD, Johns Hopkins University, Baltimore, MD, USA, dgaskin1@jhu.edu
- Jennifer Manly, PhD, Columbia University, New York City, NY, USA, jjm71@columbia.edu
- Mitchell S.V. Elkind, MD, Columbia University, New York City, NY, USA, mse13@cumc.columbia.edu
- Ralph L. Sacco, MD, MS, University of Miami, Miami, FL, USA, RSacco@med.miami.edu
- Tim Hughes, PhD, Wake Forest School of Medicine, Winston-Salem, NC, tmhughes@wakehealth.edu
- Susan Heckbert, MD, PhD, University of Washington, Seattle, WA, heckbert@uw.edu
- Deborah A. Levine, MD, MPH, University of Michigan, Ann Arbor, MI, USA, deblevin@umich.edu

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

First author: James F Burke MD, MS
Address: University of Michigan Medical School
Department of Neurology
North Campus Research Complex,
2800 Plymouth Road, Building 14, Room G105
Ann Arbor, MI 48109-2800

Phone: (734) 764-5871 Fax:
E-mail: jamesbur@med.umich.edu

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).

Name: Rebecca Gottesman, MD, PhD
Address: Building 10, Room B1D733
10 Center Drive
Bethesda, MD 20814

Phone: (301) 435-9321 Fax:
E-mail: Rebecca.gottesman@nih.gov

3. Timeline: We will complete the paper by December 2021. We anticipate it will not take considerable time to estimate these models. Once models are run, they will be incorporated into MICROSIM and disseminated as part of the MICROSIM codebase on GitHub as well as an appendix to the MICROSIM development paper.

4. Rationale:

High BP, particularly in mid-life, increases the risk for cognitive decline and dementia. High BP is a common vascular risk factor and a leading contributor to racial/ethnic disparities in health. Existing trial data provide only limited insight into the effects of life course BP control on late-life cognition, dementia, and cardiovascular events given their short duration and limited sample of mid-life participants. At the same time, marked racial and ethnic disparities exist both in BP control and in vascular and cognitive outcomes. Yet, it is less clear how much racial disparities in BP control contribute to societal level differences in CV and cognitive outcomes.

To explore the societal impact of differing midlife BP treatment approaches, and in particular, to assess the effect on late-life racial disparities in CV and cognitive outcomes, we are building a population-level simulation model, MICROSIM, based on prior CV[1] and dementia[2] models incorporating data and estimates from a variety of population-level data sources, published risk models and meta-analyses of controlled trials. The simulation starts with a large nationally representative population of the US population and advances CV risk factors, CV outcomes, cognition, and dementia forward over time against different treatment paradigms.

The current model uses relatively crude assumptions for two elements: 1. Changing vascular risk factors over time and 2. Identifying incident dementia. Using cohort study data, we seek to enhance these assumptions to improve the overall simulation model. This model will

subsequently be used for our primary questions exploring the potential societal level outcomes with different BP control strategies and the effect of eliminating racial disparities in BP control on cognitive and cardiovascular outcomes.

The first assumption of the model is that cohort data can be used to better predict change in vascular risk factors over time. Our current assumptions use simple one-factor-at-a-time changes (i.e., SBP changes by a draw from a normal distribution with a given standard deviation). This approach does not, however, maintain the variance structure between risk factors or over time. In this proposal, we outline a simple approach to predict subsequent risk factor levels from prior risk factor levels as well as all other risk factors in the model to more realistically model changes over time while maintaining the variance structure. While many methods could be applied to this problem, we have opted for relatively simple regression models as these regression models will be incorporated into an existing simulation model built from many other moving parts to maximize the validity and reliability of the overall model.

The second assumption of the model (based on our prior published simulation[2]) is that dementia is rather crudely assigned based on population-level norms with simple adjustments for cognition and education. A more elegant and simpler approach is to use the measures of global cognitive performance (GCP) developed in the previously published BP-COG Aim 1 analyses[3] to estimate individual-level dementia risk.

5. Main Hypothesis/Study Questions:

NOTE: This is a Methods paper describing the development of an element of a larger simulation model and does not have specific Study Questions and Hypotheses. Subsequent papers will address BP COG Questions and Hypotheses.

1. To predict subsequent vascular risk factors given prior vascular risk factors and other risk factors.
2. To predict dementia from known dementia predictors and GCP

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 Population We conduct a pooled cohort analysis using individual participant data from six well-characterized American prospective cohort studies with repeated measures of BP and cognition: Atherosclerosis Risk in Communities Study (ARIC), Coronary Artery Risk Development in Young Adults Study (CARDIA), Cardiovascular Health Study (CHS), Framingham Offspring Study (FOS), Multi-Ethnic Study of Atherosclerosis (MESA) study, and Northern Manhattan Study (NOMAS) for years 1971 to 2017. We will require participants to have ≥1 measurement of each given vascular risk factor studied at or before the first measurement of cognition. For incident Dementia prediction, participants from ARIC, CHS, and FOS were used.

Statistical Analysis — Models to predict Subsequent Vascular Risk Factors and Dementia

Predicting Change in Vascular Risk Factors over Time in the BP COG cohort for application in MICROSIM:

For each vascular risk factor (SBP, DBP, HDL, LDL, total cholesterol, triglycerides, creatinine, physical activity, BMI, waist circumference) and risk factor treatment (count of BP medications, statins, other lipid-lowering medications), we will develop multi-level regression models. Each regression model will include lagged values of all other vascular risk factors as well as patient age, gender, and time from baseline measurement as covariates. For prior values of the risk factor being modeled, we will also include a mean value of all prior measurements as a covariate. A random participant level intercept will be included in each model. An appropriate modeling framework will be selected in the form of the risk factor being studied (e.g., logistic regression for binary factors, linear regression for continuous variables, and Poisson for count variables). We will explore log transformation of outcomes, as needed, to optimize model fit and assess regression assumptions. Models will be fit in Python using the stats model to incorporate model outputs into MICROSIM easily. Data from all cardiovascular cohorts (ARIC, CARDIA, CHS, FOS, MESA, and NOMAS) will be included in these models. In MICROSIM, each regression model will be used to estimate subsequent values of each vascular risk factor serially over time.

Predicting Incident Dementia in the BP COG cohort for application in MICROSIM:

We will use a similar approach for dementia, although in a limited set of cohorts —ARIC, CHS, and FOS. We did not use CARDIA and MESA because few dementia cases have been ascertained. We did not use NOMAS because they have not ascertained dementia yet.

First, we will define GCP for each respondent using the approach previously developed in BP-COG and previously published.[3] In brief, this approach harmonized all cognitive measures across the 6 cardiovascular cohorts to using item response theory methods such that each individual can be assigned an overall value for their level of cognitive performance. These models are then applied in the simulation for each person in the study. GCP is estimated by first assigning a draw from the random intercept distribution of the published model. Then the product of each patient characteristic and regression coefficient is summed with the random intercept to define individual level GCP. Within the simulation, then, each simulated individual's baseline GCP and GCP slope can be readily calculated.
Using pooled individual participant data from ARIC, CHS, and FOS data in the BP COG cohort, we propose building a Cox proportional hazard model to estimate the probability of dementia in a given year using baseline GCP and GCP slope in addition to known dementia predictors so that individual-level dementia risk can be estimated using GCP. Specifically, we will build Cox a proportional hazards model including baseline GCP, GCP slope, age, gender, race, cohort, and education and predicting time to adjudicated dementia diagnosis. Coefficients and baseline hazard data from this model will be incorporated into MICROSIM to assign the risk of dementia for each simulated patient each year.

References:

1. Sussman J, Vijan S, Hayward R. Using benefit-based tailored treatment to improve the use of antihypertensive medications. *Circulation.* 2013;128(21):2309-2317.
2. Burke JF, Langa KM, Hayward RA, Albin RL. Modeling Test and Treatment Strategies for Presymptomatic Alzheimer Disease. *PLOS ONE.* 2014;9(12):e114339.
3. Levine DA, Gross AL, Briceño EM, et al. Association Between Blood Pressure and Later-Life Cognition Among Black and White Individuals. *JAMA neurology.* 2020;77(7):810-819.

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/aricproposals/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)?
No proposals seem clearly related.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes _X_No

11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study (list number* _____)
___ 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.

We understand this.

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.
We understand this.