ARIC Manuscript Proposal # 3609

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

1.a. Full Title: Using Information from Multiple Cohort Studies to Simulate and Extend SPRINT-MIND: What Would the Effect of Intensive Blood Pressure Treatment on Prevention of Dementia Have Been If the Trial Had Not Been Terminated Early?

b. Abbreviated Title (Length 26 characters): Simulating SPRINT-MIND

2. Writing Group:

Writing group members (by alphabetical order): Sarah Ackley, Erin Bennett, Annette Fitzpatrick, Kan Z. Gianattasio, M. Maria Glymour, Rebecca Gottesman, Deborah A. Levine, Lenore Launer, Megha L. Mehrotra, Melinda C. Power (last), Jingkai Wei (first), Scott C. Zimmerman

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

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3. Timeline: 1 year from approval

4. Rationale:

Hypertension has been recognized as an important risk factor of cognitive impairment based on observational data.[1-3] It has therefore been hypothesized that reducing blood pressure may lower the risk of dementia.[4] However, randomized trials have not demonstrated benefits for reducing the risk of dementia through reducing blood pressure.[5,6] The Systolic Blood Pressure Intervention Trial – Memory and Cognition in Decreased Hypertension (SPRINT-MIND) attempted to test whether intensive blood pressure control reduces the risk of mild cognitive impairment and dementia.[7] The SPRINT-MIND trial included 9,361 (mean age: 67.9 years, 35.6% women) individuals who had a systolic blood pressure (SBP) between 130 and 180 mm Hg and cardiovascular disease (defined as having clinical or subclinical cardiovascular disease, chronic kidney disease, or a Framingham Risk Score ≥15, or age ≥75 years). Participants were randomly assigned to intensive treatment group (with the goal of less than 120mmHg) or standard treatment group (with the goal of less than 140mmHg). After a median follow-up of 5.1 years, intensive blood pressure control reduced the incidence of mild cognitive impairment but not dementia. The results showed that intensive control of blood pressure reduces risk of mild cognitive impairment, while no effect was shown on risk of dementia, although the trial was terminated early because the parent study, SPRINT, demonstrated benefit on the primary endpoint.

Due to its early termination, the effect of intensive blood pressure control on incident dementia over the initially planned follow-up of SPRINT-MIND (6 to 8 years, depending on time of enrollment) was not determined. To answer this question, we aim to simulate the continued SPRINT-MIND trial using information from observational studies to (1) demonstrate whether or not we can recover the results of the SPRINT-MIND trial, and (2) extend the simulation to demonstrate what we would have seen had SPRINT-MIND continued to its original end date to estimate the effect of intensive blood pressure control on reducing risk of dementia. The Atherosclerosis Risk in Communities study (ARIC) is one of the most important studies that have information on change of blood pressure and dementia, and a combined population of ARIC with two other cohorts with similar age and relevant exposure and outcome assessments (Cardiovascular Health Study (CHS), Health and Retirement Study (HRS)) will enable the simulated trial to have sufficient statistical power.

5. Main Hypothesis/Study Questions:

We hypothesize that intensive blood pressure control (with the goal of achieving and/or maintaining systolic blood pressure (SBP)<120 mmHg) would have achieved reduced incident dementia after 6 to 8 years, compared to standard blood pressure control (with the goal of achieving and/or maintaining systolic blood pressure (SBP)<140 mmHg) had SPRINT-MIND not been terminated early.

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).

ARIC has blood pressure measurements and assessment of dementia available throughout all visits of the Neurocognitive Study (visit 5: 2011-2013, visit 6: 2016-2017, visit 7: 2018-2019). We will use the information on blood pressure and dementia, as well as other potential covariates

(described below) for the proposed analysis. Similarly, we will use relevant information available in CHS and HRS.

To emulate the SPRINT-MIND trial, we will create a simulated dataset with follow-up visits every 2 years based on information from three cohort studies. (ARIC, baseline (visit 5), +2 years (imputed), +4 years (visit 6), + 6 years (visit 7); mean age at baseline: 76 years), Cardiovascular Health Study (CHS, baseline (CHS baseline), +2 years (CHS Year 3), +4 years (CHS Year 5), + 6 years (CHS Year 7)); mean age at baseline: 75 years), and Health and Retirement Study (CHS, baseline (HRS Year 2000), +2 years (HRS Year 2002), +4 years (HRS Year 2004), + 6 years (HRS Year 2006)); median age at baseline: 72 years). Participants with systolic blood pressure<110 mmHg, diabetes, organ transplant, certain renal diseases (polycystic kidney disease, end-stage renal disease), recent cardiovascular events, history of stroke, or other medical conditions that affect survival before the end of trial will be excluded from each cohort.

Directed acyclic graphs (DAGs) will be created for the overall causal relationship between blood pressure control and dementia. Common variables, including age, sex, education, race/ethnicity, smoking, and blood pressure are available in all three cohorts, and dementia was assessed in both ARIC and CHS. All three studies will be pooled (Figure 1), and missing information, including structurally missing data, will be imputed in the pooled sample. Subjects will be classified into intensive blood pressure control (with average systolic blood pressure=110 mmHg), and normal blood pressure control (with average systolic blood pressure=130 mmHg) after 4 years. We will then use the DAG as a roadmap to derive a series of simulation rules for dementia outcomes and other covariates in follow-up visits. We will then use these simulation rules to simulate data corresponding to SPRINT-MIND, starting from a sample identical to that of the SPRINT-MIND in terms of age, gender, and race/ethnicity based on baseline SPRINT-MIND data obtained through BIOLNCC. In this simulated sample, we will estimate hazard ratios over a follow-up period consistent with SPRINT-MIND. We will compare these to the reported hazard ratios, and, if the results are consistent, compute effect estimates of longer intervention, starting with the originally planned trial length. Additional methods to adjust for differences in study populations (e.g. inverse probability weighting) will be applied if the results are not consistent with the SPRINT-MIND study.

Variables list
Non-modifiable variables:

	CHS	ARIC	HRS
Age	available	available	available
Sex	available	available	available
Race/ethnicity	available	available	available
Education	available	available	available

Lifestyle factors:

	CHS	ARIC	HRS
	Baseline		
Ever Smoking	Available	Available	Available
Dietary intake	Available	Needs to be imputed from visit 1 & 3 of the	Needs to be imputed from CHS &ARIC

		ARIC study (collected with FFQ)	
Physical activity	Available	Available	Available
	+2 years		
Ever Smoking	Available	Available	Available
Dietary intake	Needs to be imputed from Year 1 of CHS	Needs to be imputed from Year 1	Needs to be imputed from CHS &ARIC
Physical activity	Needs to be imputed from Year 1 of CHS	Needs to be imputed from Year 1 of ARIC	Available
	+4 years		
Ever Smoking	Available	Available	Available
Dietary intake	Available	Needs to be imputed from Year 1	Needs to be imputed from CHS &ARIC
Physical activity	Available	Available	Available
	+ 6 years		
Ever Smoking	Available	Available	Available
Dietary intake	Needs to be imputed from Year 5 of CHS	Needs to be imputed from Year 1	Needs to be imputed from CHS &ARIC
Physical activity	Needs to be imputed from Year 5 of CHS	Available	Available

Other physical conditions:

	CHS	ARIC	HRS
	Baseline		
Total cholesterol	Available	Available	Needs to be imputed from CHS & ARIC
HDL-C	Available	Available	Needs to be imputed from CHS & ARIC
LDL-C	Available	Available	Needs to be imputed from CHS & ARIC
Chronic kidney disease	Available	Available	Needs to be imputed from CHS & ARIC
Antihypertensive medication	Available	Available	Available
	+2 years		
Total cholesterol	Available	Needs to be imputed from Year 1 of ARIC	Available
HDL-C	Needs to be imputed from Year 1 of CHS	Needs to be imputed from Year 1 of ARIC	Available
LDL-C	Needs to be imputed from Year 1 of CHS	Needs to be imputed from Year 1 of ARIC	Needs to be imputed from CHS & ARIC
Chronic kidney disease	Available	Available	Needs to be imputed from CHS & ARIC
Antihypertensive medication	Available	Available	Available
	+4 years		
Total cholesterol	Available	Available	Available
HDL-C	Needs to be imputed from Year 1 of CHS	Available	Available

LDL-C	Needs to be imputed from Year 1 of CHS	Available	Needs to be imputed from CHS & ARIC
Chronic kidney disease	Available	Available	Needs to be imputed from CHS & ARIC
Antihypertensive medication	Available	Available	Available
	+ 6 years		
Total cholesterol	Available	Available	Available
HDL-C	Needs to be imputed from Year 1 of CHS	Available	Available
LDL-C	Needs to be imputed from Year 1 of CHS	Available	Needs to be imputed from CHS & ARIC
Chronic kidney disease	Available	Available	Needs to be imputed from CHS & ARIC
Antihypertensive medication	Available	Available	Available

Blood pressure:

	CHS	ARIC	HRS
	Baseline		
SBP	Available	Available	Available
	+2 years		
SBP	Available	Available	Available
	+4 years		
SBP	Available	Available	Available
	+ 6 years		
SBP	Available	Available	Available

Dementia:

	CHS	ARIC	HRS
	Baseline		
Dementia	Available	Available	To be derived from cognition test and demographic factors
	+2 years		
Dementia	Available	Available	To be derived from cognition test and demographic factors
	+4 years		
Dementia	Available	Available	To be derived from cognition test and demographic factors
	+ 6 years		
Dementia	Available	Available	To be derived from cognition test and demographic factors

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? __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 current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes __X__ 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

_____ 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)?

3051 Walker at al. The association of middle and late-life blood pressure with conversion to MCI and dementia: The ARIC Study
3163 Hodis et al. Association of hypertension according to new ACC/AHA blood pressure guidelines with incident dementia in the ARIC cohort.
3041 Launer et al. Preventing dementia: The case of elevated blood pressure in older persons - What to treat with?
#2175 Gottesman et al. Midlife blood pressure and 20-year cognitive change: The ARIC Neurocognitive Study
#734 de Moraes et al. Blood pressure over time and changes in cognitive function
#3069

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* __2017.01_____)

___ 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.

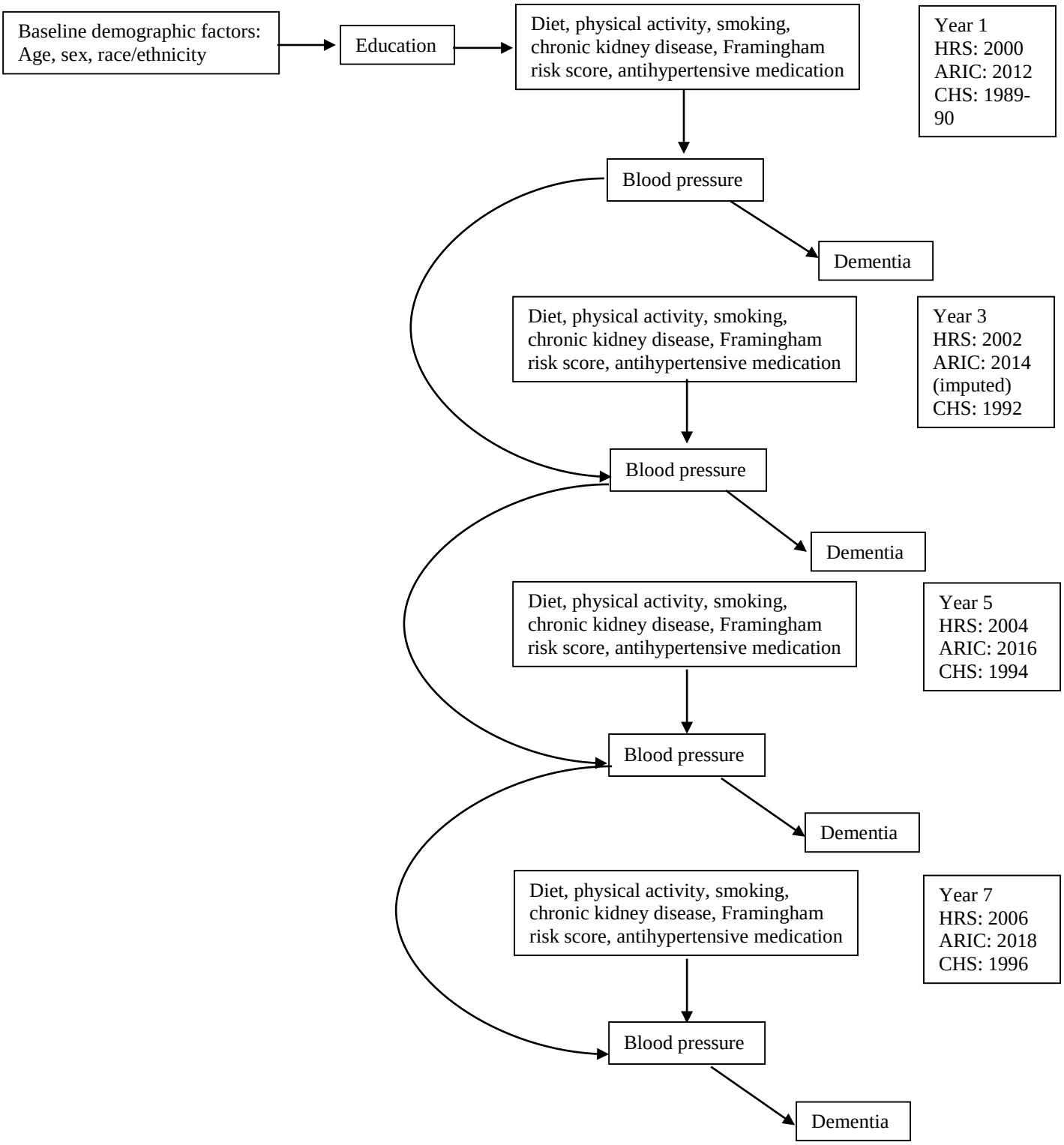

Figure 1. Diagram for the data to be used to create the data-generating rules for SPRINT-MIND

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3. Tzourio C, Dufouil C, Ducimetiere P, Alperovitch A. Cognitive decline in individuals with high blood pressure: a longitudinal study in the elderly. EVA Study Group. Epidemiology of Vascular Aging. *Neurology.* 1999;53(9):1948-1952.
4. Tzourio C. Hypertension, cognitive decline, and dementia: an epidemiological perspective. *Dialogues Clin Neurosci.* 2007;9(1):61-70.
5. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *Jama.* 1991;265(24):3255-3264.
6. Prince MJ, Bird AS, Blizard RA, Mann AH. Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's trial of hypertension in older adults. *Bmj.* 1996;312(7034):801-805.
7. Group SMIftSR, Williamson JD, Pajewski NM, et al. Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial. *JAMA.* 2019;321(6):553-561.