ARIC Manuscript Proposal Form

ARIC Publication Admin Use Only

Publication Committee Review Date: **6/11/24**
ARIC Manuscript Proposal Number: **# 4480**

1.a. Full Title: Modulation of Genetic Risk for Dementia by Blood Pressure

b. Abbreviated Title (Length 26 characters): BP modulation of Dementia PRS

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
Writing group members: First Author: Valerie N. Morrill
Other Authors: James Pike, Myriam Fornage, David Knopman, Thomas Mosley, Josef Coresh, Andrea L.C. Schneider, Adrienne Tin
Last Author: Rebecca F. Gottesman

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

First author [please provide a middle initial; EX: Adam L Williams]:

Valerie	**N**	**Morrill**
First name	Middle initial	Last name

Address: Building 10, Room 4D37, 10 Center Drive, Bethesda, MD 20814

Phone:781-835-6210
E-mail:valerie.morrill@nih.gov

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (The ARIC author should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).

Name: Dr. Rebecca F. Gottesman
Address: Building 10, Room 4D37, 10 Center Drive, Bethesda, MD 20814

Phone: 301-435-9321
E-mail: rebecca.gottesman@nih.gov

3. Timeline:Manuscript prepared and submitted in ~5-6 months.

4. Rationale:

Alzheimer's disease (AD) is the most common form of dementia, resulting in cognitive decline that impacts daily functioning for over 6.7 million Americans[1, 2]. There have been many studies on potential targets for dementia prevention, including by the Lancet Commission, which identified hypertension as one of twelve modifiable risk factors [3]. Reducing hypertension to improve dementia outcomes may be effective because it is highly prevalent in the United States, affecting nearly half of adults by midlife[4]. In the ARIC study, hypertension in midlife, but not in late life, has been associated with dementia risk[5], and cognitive decline[6] over 30 years of follow up.

It is also well established that genetics represent a non-modifiable risk factor for dementia. Twin studies have estimated the heritability of AD to be between 60-80%[7]. Carrier status of the APOEe4 allele has been described as a significant genetic contributor to dementia for over 30 years[8]. More recently, large genome wide association studies (GWAS) have described 83 independent risk loci in a European population[9] and 12 independent loci in an African ancestry population[10] that are associated with dementia. Dementia polygenic risk scores (PRS), continuous scores that capture an individual's genetic predisposition, have been used to stratify individuals into genetic risk categories[9, 11, 12]. In ARIC, higher dementia PRS strata were associated with dementia in both European and African ancestry populations [11].

Although genetics is a non-modifiable risk factor, individuals with a genetic predisposition for dementia may still be able to prevent or delay dementia with blood pressure control. However, the extent to which blood pressure modulates genetic risk for dementia, as defined by PRS, is unknown. Other studies have examined whether the association between hypertension and dementia differs by APOEe4 allele carrier status with mixed results[13, 14] [5, 15]. Our study will benefit from using a PRS, which captures more genetic variation, to define genetic risk groups. Using a similar study design to this proposal, Adrienne Tin and colleagues evaluated whether the association between Life's Simple 7 (LS7) and dementia differs across dementia PRS strata in ARIC. LS7 is a measure of healthy lifestyle factors, including blood pressure. Higher LS7 scores were associated with a decreased risk of dementia within all PRS strata for individuals with European ancestry. The effect was similar in individuals with African ancestry but not statistically significant, likely due to a smaller sample size and a less powerful PRS[11]. Our study will examine hypertension and antihypertension treatment specifically instead of using a lifestyle summary score.

This study aims to determine how blood pressure and its control modulates lifetime risk of dementia for individuals at high genetic risk. Effectively communicating the impact of modifiable risk factors across PRS strata could help inform personal prevention strategies.

5. Main Hypothesis/Study Aims

Main Objectives: Determine how measured midlife blood pressure modifies genetic risk for dementia

1. Determine the association between genetic risk (PRS tertiles) and incident dementia

2. Determine the association between midlife blood pressure groups and incident dementia within each PRS strata
3. Determine the lifetime risk of dementia within each of the 12 (3 PRS*4 blood pressure) groups

Secondary Objectives: Determine how hypertension treatment modifies genetic risk for dementia

1. Among participants with stage 1 or 2 hypertension, determine the association between treatment and incident dementia within each PRS strata
2. Among participants with stage 1 or 2 hypertension, determine the lifetime risk of dementia within each of the 6 (3 PRS*2 treatment) groups

6. Design and analysis - please address the following aspects:

a) inclusion/exclusion
b) study design
c) outcome and other variables of interest with specific reference to the time of their collection
d) summary of data analysis
e) Any anticipated methodologic limitations or challenges if present

Inclusion/Exclusion criteria:
Among 15,792 ARIC participants enrolled at baseline, we will include participants who are free of dementia at age 50.

We will exclude participants who have missing genetic data, missing blood pressure data from visit 1, or missing dementia status. We will also exclude participants who did not consent to share their DNA, do not pass genetic QC, or do not have European or African genetic ancestry.

Study design:
Longitudinal cohort design with age 50 as the baseline and age as the time scale.

All analyses will be stratified by genetic ancestry (European, African), and then meta-analyzed to obtain overall estimates.

Outcome variables:

Incident Dementia
Dementia during follow up until 2020 (or later, depending on what data are available as of the date of manuscript preparation) will be defined using the level 3 dementia diagnosis, and we will use age at level 3 dementia diagnosis or censorship as our time variable.

Exposure variables:

Genetic Risk Category
We will assign tertiles of genetic risk for dementia using genetic ancestry specific (European and African) PRS. We will use precalculated PRS if there are suitable dementia or AD PRS already

calculated in ARIC. We would use a pre calculated PRS if it was calculated on our entire study sample, used the most recent ancestry specific GWAS results, and was calculated separately for European and African ancestries. If not, we will derive our own using the steps below:

Genetic quality control, PC generation, genetic ancestry assignment, and imputation procedures will be based off recent studies that generated PRS in ARIC[11, 16]. First, genetic quality control will exclude individuals with a call rate of <0.95, duplicates, and gender mismatches using PLINK. Then, principal components of ancestry will be calculated, and genetic ancestry will be assigned using PLINK. Genetic outliers based on principal components of ancestry will be excluded. We will impute missing genotypes if necessary to capture the genetic variants in the PRS using the Michigan Imputation server. We will exclude imputed variants with imputation quality <0.3.

Ancestry specific PRS will be generated from genomewide significant variants with the goal of ease of interpretability and replication for future analyses[17]. Risk alleles and weights will be identified in the latest European ancestry[9] and African ancestry[10] GWAS for Alzheimer's Disease. The European Ancestry GWAS identified 83 genomewide significant variants among the European Alzheimer & Dementia Biobank and the UK Biobank. The African ancestry GWAS identified 12 genomewide significant variants among the Million Veteran Program. To calculate ancestry specific PRS for the ARIC participants, the number of AD risk alleles will be multiplied by the published log OR for each genetic variant using PLINK. We will then assign individuals to tertiles of genetic risk for dementia.

If we are underpowered to examine interactions between PRS tertiles and blood pressure category, we will also define genetic risk using the dementia PRS as a continuous measure.

Blood Pressure Risk Category

Sitting systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels were assessed at visit 1 using three readings with >30 seconds between each reading. SBP and DBP were defined as the mean of measurements two and three. Our primary definition of blood pressure category at baseline will use the most recent American College of Cardiology/American Heart Association Task Force guidance from 2017 [18]:

Blood Pressure Category	Systolic Blood Pressure		Diastolic Blood Pressure
Healthy	<120 mmHg	and	<80 mmHg
Elevated	120-129 mmHg	and	<80 mmHg
Stage 1 Hypertension	130-139 mmHg	or	80-89 mmHg
Stage 2 Hypertension	>=140 mmHg	or	>=90 mmHg

Our secondary definition of blood pressure category will further stratify individuals with stage 1 or stage 2 hypertension by antihypertensive use at baseline.

Covariates:

Covariates in minimally adjusted models will include decade of birth (1920-29/1930-39/1940+), sex, center and education. To account for confounding by genetic ancestry subpopulations, we

will also include up to 10 principal components of ancestry. We will determine how many principal components to include as covariates by sequentially adding principal components and assessing the cumulative variance explained.

Fully adjusted models will also include visit 1 body mass index, total cholesterol, high-density lipoprotein cholesterol, cigarette smoking status (current/former/never), alcohol consumption status (current/former/never), prevalent diabetes (fasting glucose value >=126mg/dL, non-fasting glucose value >=200 mg/dL, or using medication for diabetes), coronary heart disease (self-reported), and previous stroke (self-reported). We will not adjust for APOEe4 carrier status because it is captured within the PRS.

Other Variables:
We will use time to death for sensitivity analyses described below.

Data Analysis:
All analyses will be stratified by genetic ancestry (European and African), and then meta-analyzed to obtain overall estimates.

Participant characteristics will be described across blood pressure categories and across genetic risk categories.

To address hypothesis 1, one Cox proportional hazards model will be used to estimate the association between PRS tertile and dementia with the bottom tertile as the reference group.

To address hypothesis 2, three Cox proportional hazards models (stratified by PRS tertile) will be used to estimate the association between blood pressure category and dementia with healthy blood pressure as the reference group. In addition, one Cox proportional hazards model will be used to formally test the interaction between PRS tertile and blood pressure category. In a secondary analysis among participants with hypertension, three Cox proportional hazards models (stratified by PRS tertile) will be used to estimate the association between treatment and dementia with untreated as the reference group. In addition, one Cox proportional hazards model will be used to formally test the interaction between PRS tertile and treatment.

To address hypothesis 3, one competing-risks regression model will be used to estimate the lifetime risk of dementia adjusting for the competing risk of death within each of the 12 (3 PRS*4 blood pressure) groups. We will use a competing-risks regression model based on Fine and Gray's proportional subhazards model with age as the time scale, and baseline at 50 years old. We will investigate statistically significant differences in lifetime risk of dementia between groups, and interactions between PRS tertile and blood pressure groups using Irwin's restricted mean. In a secondary analysis among participants with hypertension, one competing-risks regression model will be used to estimate the lifetime risk of dementia adjusting for the competing risk of death within each of the 6 (3 PRS*2 treatment) groups. Differences in lifetime risk of dementia between groups, and interactions between PRS tertile and treatment will be investigated using Irwin's restricted mean.

Cox proportional hazards model assumptions will be evaluated using Schoenfeld residuals. Each of the models described will be adjusted minimally and then fully adjusted with the covariates described above.

Sensitivity Analyses to address anticipated challenges:

Early neurodegeneration may lead to lower blood pressure. We will perform a sensitivity analysis of hypothesis 2 with a 5-year lag.

Participants may change blood pressure groups over time. We will make tables of blood pressure groups across Visits 1-4 to determine if participants change blood pressure group frequently. If so, we will perform a sensitivity analysis of hypothesis 2 and 3 using a time averaged blood pressure measure to assign blood pressure group.

f) Will the author need Limited data to complete the proposed manuscript? ☒ Yes, Limited data is needed (Provide a brief (2-3 sentences) justification for requesting PHI data) . ☐ No, De-identified data will be sufficient.

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

If we derive the PRS ourselves we will need the genomic data to define one of our main exposures.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? (Non-ARIC analysis means that the authors are not regarded as ARIC investigators and the "ARIC author" is essentially just a facilitator rather than an integral part of the writing group.) ☐ Yes ☒ 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 is distributed to ARIC PIs annually, 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 ☐ 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 or the "sponsoring" ARIC 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 website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website Publications Proposal Search]

☒ 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)?

- MP # 3677: An Evaluation of Life's Simple 7 Score in Midlife in Offsetting the Genetic Risk of Dementia
- MP #3811: Genetic Risk, Midlife Life's Simple 7 And Incident Ischemic Stroke In the Atherosclerosis Risk In Communities Study
- MP #3581: The Moderating Influence of Education and Lifestyle on Genetic Risk for Dementia
- MP #3051: The association of middle and late-life blood pressure with conversion to MCI and dementia: The ARIC Study
- MP #4251: Profiling plasma proteins correlated with polygenic risk for Alzheimer's disease

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)? ☐ Yes ☒ No → Skip to question 12

11.b. If yes to 11.a., is the proposal

☒ **A. primarily the result of an ancillary study**

☐ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)**

11.c. If yes to 11.a., list number* 2008.06__

*ancillary studies are listed by number https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website Ancillary Studies 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.
Understood.

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 https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website Publications Publication Policies, Forms, and Guidelines].

http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

To view publications materials, click "Log in" at the top right of the ARIC website. Click "Forgot Password" if you are experiencing issues with logging in.

References:

1. Collaborators, G.U.N.D., et al., *Burden of Neurological Disorders Across the US From 1990-2017: A Global Burden of Disease Study.* JAMA Neurol, 2021. **78**(2): p. 165-176.
2. *2023 Alzheimer's disease facts and figures.* Alzheimers Dement, 2023. **19**(4): p. 1598-1695.
3. Livingston, G., et al., *Dementia prevention, intervention, and care: 2020 report of the Lancet Commission.* Lancet, 2020. **396**(10248): p. 413-446.
4. Ostchega, Y., et al., *Hypertension prevalence among adults aged 18 and over: United States, 2017–2018.* NCHS Data Brief, 2020. **364**.
5. Walker, K.A., et al., *Association of Midlife to Late-Life Blood Pressure Patterns With Incident Dementia.* JAMA, 2019. **322**(6): p. 535-545.
6. Gottesman, R.F., et al., *Midlife hypertension and 20-year cognitive change: the atherosclerosis risk in communities neurocognitive study.* JAMA Neurol, 2014. **71**(10): p. 1218-27.
7. Gatz, M., et al., *Role of genes and environments for explaining Alzheimer disease.* Arch Gen Psychiatry, 2006. **63**(2): p. 168-74.
8. Saunders, A.M., et al., *Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease.* Neurology, 1993. **43**(8): p. 1467-72.
9. Bellenguez, C., et al., *New insights into the genetic etiology of Alzheimer's disease and related dementias.* Nature genetics, 2022. **54**(4): p. 412-436.
10. Sherva, R., et al., *African ancestry GWAS of dementia in a large military cohort identifies significant risk loci.* Mol Psychiatry, 2023. **28**(3): p. 1293-1302.
11. Tin, A., et al., *Genetic Risk, Midlife Life's Simple 7, and Incident Dementia in the Atherosclerosis Risk in Communities Study.* Neurology, 2022. **99**(2): p. e154-e163.
12. Yu, C., et al., *Validation of newly derived polygenic risk scores for dementia in a prospective study of older individuals.* Alzheimers Dement, 2023. **19**(12): p. 5333-5342.
13. Andrews, S., et al., *Interactive effect of APOE genotype and blood pressure on cognitive decline: the PATH through life study.* J Alzheimers Dis, 2015. **44**(4): p. 1087-98.
14. de Frias, C.M., K.W. Schaie, and S.L. Willis, *Hypertension moderates the effect of APOE on 21-year cognitive trajectories.* Psychol Aging, 2014. **29**(2): p. 431-9.
15. Gottesman, R.F., Albert, M.S., Alonso, A., Coker, L.H., Coresh, J., Davis, S.M., Deal, J.A., McKhann, G.M., Mosley, T.H., Sharrett, A.R. and Schneider, A.L., *Associations Between Midlife Vascular Risk Factors and 25-Year Incident Dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort.* JAMA Neurology, 2017. **74**(10): p. 1246-1254.
16. Thomas, E.A., et al., *Polygenic Risk, Midlife Life's Simple 7, and Lifetime Risk of Stroke.* J Am Heart Assoc, 2022. **11**(15): p. e025703.
17. Khera, A.V., et al., *Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease.* N Engl J Med, 2016. **375**(24): p. 2349-2358.
18. Whelton, P.K., et al., *2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.* Circulation, 2018. **138**(17): p. e484-e594.