ARIC Manuscript Proposal #3927

PC Reviewed: 9/14/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Maintenance of normal blood pressure from mid- to late-life in the Atherosclerosis Risk in Communities Study: Implications for cardiovascular disease prevention

b. Abbreviated Title (Length 26 characters): Maintenance of normal BP in ARIC

2. Writing Group:

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

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3. Timeline: We plan to initiate the study following approval of our proposal (anticipated in September 2021). We plan to submit the manuscript for publication within approximately 6 months. The anticipated timeline is as follows:

Prepare dataset and perform data management	2 weeks
Conduct data analyses	4 weeks
Prepare draft tables and figures	4 weeks
Prepare draft manuscript	4 weeks
Obtain co-author input on manuscript	2 weeks
Revise manuscript	2 weeks
Obtain additional feedback on manuscript	2 weeks
Prepare manuscript for journal submission	2 weeks

4. Rationale:

In most industrialized settings, such as the United States, the mean systolic blood pressure increases with age. In contrast, in certain non-industrialized populations, mean systolic blood pressure is not higher at older age.[1–3] This suggests that the increase in systolic blood pressure that typically occurs as people age in many settings may be preventable. The risk for cardiovascular disease (CVD) increases with higher blood pressure, beginning at levels below the threshold for hypertension.[4] Therefore, maintaining normal blood pressure, systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg, without the use of antihypertensive medication can contribute to CVD prevention. One study estimated that almost 40% of the 2.85 million CVD events that occur in the Unites States annually are attributable to blood pressure levels above the normal range and therefore could be avoided with the maintenance of normal blood pressure.[5]

A cross-sectional analysis from the National Health and Nutrition Examination Survey estimated that 5.0% of US adults ≥75 years of age have normal blood pressure (Muntner et. al., in preparation). Identifying characteristics of individuals who maintain normal blood pressure over their life course into old age may inform interventions to prevent the rise in blood pressure with aging that occurs for most US adults.

A recent, longitudinal analysis of the Jackson Heart Study by Hardy et. al., followed participants across 3 study visits over a median of 8 years to determine the proportion who maintained normal blood pressure, associated lifestyle and psychosocial factors, and incidence of CVD.[6] The study found that just 757 of 3432 participants (22.1%) had normal blood pressure at baseline (mean age 46.4 years), and of those, only 262 (34.6%) maintained normal blood pressure across all follow-up visits. Having and maintaining a normal body mass index and ideal levels of physical activity, as defined by the American Heart Association's Life's Simple 7, during follow-up were associated with maintaining normal blood pressure. Over a median follow-up of 6 years, the incidence of CVD was 4.5, 6.3, and 16.4 per 1000 person-years among participants who maintained normal blood pressure across all visits, had normal blood pressure at baseline but did not maintain it, and had elevated blood pressure or hypertension at baseline, respectively.

This study was limited by short periods used to assess the maintenance of normal blood pressure and CVD events.

The Atherosclerosis Risk in Communities (ARIC) Study is well-positioned to build on these studies and others which have examined blood pressure patterns through mid-life[7,8] to characterize the maintenance of normal blood pressure from mid-life to late-life and determine the association with outcomes that may be affected by blood pressure patterns and are important to older adults, including maintaining functional independence and cognition, as well as CVD. The proposed research extends previous work conducted in ARIC. Pretruski-Ivleva et. al. (2016) examined blood pressure trajectories using latent class growth models from ARIC visits 1-4 and the incidence of CVD following visit 4.[9] Ongoing work is examining the association of baseline blood pressure with change in physical function from Visit 6 to Visit 7.[10] A 2019 publication by Walker et. al., examined 24-year longitudinal blood pressure patterns from visit 1 to visit 5 and associations with incident dementia.[11] In this study, mid-life normotension was defined as not having 2 consecutive visits during visits 1-4 with hypertension (blood pressure ≥140/90 mmHg or taking antihypertensive medication) and having late-life normotension, defined as not having hypertension at visit 5. Thus, participants could be considered to have normotensive blood pressure despite having levels above the current guideline definition of normal. Furthermore, data are now available from ARIC visits 6 and 7 to examine blood pressure patterns over a longer time period and at older ages.

Our aims are to: 1) determine the proportion of individuals who maintain normal blood pressure during mid-life and who maintain normal blood pressure from mid-life through late-life; 2) compare the characteristics of those who maintain normal blood pressure from mid- to late life, those who have normal blood pressure in mid-life but do not maintain it in late-life, and those who do not have normal blood pressure in mid-life; and 3) examine the association of blood pressure maintenance categories with outcomes including poor physical function and incidence of dementia and CVD.

5. Main Hypothesis/Study Questions:

Aim 1: To determine the proportion of individuals who maintain normal blood pressure through mid-life and who maintain normal blood pressure through mid-life and late-life.

Hypothesis: We hypothesize that only a small proportion of participants will have normal blood pressure at all ARIC visits in mid-life (Visits 1-4) and in late-life (Visits 5-7).

Aim 2: To compare the characteristics of participants with normal blood pressure in mid-life who do and do not maintain normal blood pressure into late-life.

Hypothesis: We hypothesize that having and maintaining a normal body mass index, higher physical activity levels, and a healthy dietary pattern will be associated with maintenance of normal blood pressure from mid- to late-life.

Aim 3: To examine the association of blood pressure maintenance categories with physical function in late-life and the incidence of dementia and CVD.

Hypothesis: We hypothesize maintaining normal blood pressure from mid- to late-life will be associated with better physical function and a lower incidence rate of dementia and CVD

compared to those who have normal blood pressure in mid-life but not in late-life, and those who do not have normal blood pressure in mid-life.

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

Inclusion criteria: The study population will include adults who attended at least 4 study visits, including 1 or more of ARIC Visits 5-7, and who attended at least one visit when they were at least 75 years of age (Table).

Exclusion criteria: We will exclude participants who are non-white and non-Black.

Study population	**N**
White or Black participants who attended ≥4 visits (i.e., had BP measurements at ≥ 4 visits)	11488
+ Attended ≥1 of Visit 5, 6, or 7 (i.e., had blood pressure measurements from ≥1 of these visits)	6546
+ Attended ≥1 visit when they were ≥75 years of age	5631

Maintenance of normal blood pressure from mid-life to late-life

Normal blood pressure will be defined as: measured systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg, and not taking antihypertensive medication based on self-report. Systolic and diastolic blood pressure values are based on the mean of the second and third blood pressure readings, except at Visit 4 where we will use the mean of the first and second readings because only two measurements were obtained.

The table below indicates the visits from which mid-life and late-life blood pressure will be determined. We will use all available visits for participants in our study population.

	Mid-life BP				**Late-life BP**		
ARIC Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Calendar year	1987-89	1990-92	1993-95	1996-98	2011-13	2016-17	2018-19
Age of participants, years	44-66	46-70	49-73	52-75	66-90	71-94	73-96

We will categorize participants in the study population based on their blood pressure measurements as follows:

- Normal blood pressure maintained from mid-life to late life: Normal blood pressure at every visit attended (N=150)
- Normal blood pressure in mid-life, but not maintained in late-life: Normal blood pressure at all ARIC Visits 1-4 attended, but higher blood pressure or antihypertensive medication use at any of ARIC Visits 5-7 (N=1,202)

- Did not have normal blood pressure in mid-life: Blood pressure above normal or antihypertensive medication use at any of ARIC Visits 1-4 (N=4,279)

For those who did not have normal blood pressure in mid-life, we will consider identifying subgroups such as:

- Those who had hypertension (systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥80 mmHg, or taking antihypertensive medication) before age 65 years
- Those who had hypertension after, but not before, age 65 years
- Those who had elevated blood pressure, systolic blood pressure 120-129 mmHg or diastolic blood pressure <80 mmHg while not taking antihypertensive medication, but did not have hypertension.

In sensitivity analyses, we will consider alternative ways of defining maintenance of normal blood pressure in the study population. For example:

- We will assess antihypertensive medication use based on medication codes from the pill bottle review. For those with normal blood pressure taking antihypertensive medication according to the medication codes but who do not report taking medication to lower their blood pressure (e.g., an individual who is taking an ACE inhibitor because they have diabetes), we will use the formulas from Law et. al.[12] to calculate to their estimated pretreatment blood pressure based on the number and dose of antihypertensive medications being used. We will define those with estimated pretreatment blood pressure <120/80 mmHg at all visits as having normal blood pressure.
    - For example, Law et. al., estimate the effect (E) of one drug at standard dose in lowering blood pressure from a pretreatment blood pressure (P) as: E = [9.1+0.10(P−154)] systolic and E =[5.5+0.11(P−97)] diastolic.[12]
    - Therefore, P can be estimated as treated blood pressure ($P_{treated}$) + E, or P = [($P_{treated}$ – 6.3)/0.9] systolic and P = [($P_{treated}$ – 5.17)/0.89] diastolic.
- Across study visits, a rise in systolic blood pressure of <0.5 mm Hg per year of follow-up, with blood pressure <120/80 mm Hg at all visits while not taking antihypertensive medication. In industrialized settings, systolic blood pressure rises 7-15 mmHg per decade after age 40 years;[13–15] thus, our measure will identify individuals who experience an increase in systolic blood pressure less than 50% of the average. Additional exploratory analyses based on the level and slope of change in systolic blood pressure may be conducted.
- Allowing for one study visit with blood pressure above normal (≥120/80 mm Hg) without the use of antihypertensive medication, provided the participant has normal blood pressure at the last available visit.

Participant characteristics of interest

The table below describes the variables we will include in our analyses and the timing of their measurement:

Characteristic	Measurement	V1	V2	V3	V4	V5	V6	V7	Recommendation
Sociodemographic factors									

1. Age	Continuous, years	X	X	X	X	X	X	X	
2. Sex	Male/Female	X*							
3. Race/ethnicity	NHB/NHW	X*							Use NHB/NHW (as opposed to race-center) and exclude non-white and non-Black participants
4. Education	<HS, HS, vocational school, college, graduate/professional school	X*							Categorize as <HS, HS or vocational school, and at least some college or graduate/ professional school
5. APOEe4 status	0, 1, 2 alleles	X*							Categorize as 0, 1, 2
Health behaviors									
6. BMI a. Mid-life b. Change from mid- to late-life	Continuous or <25, 25-<30, ≥ 30 kg/m^2	X	X	X	X	X	X	X	a. Use V1-V4: categorize BMI as <25 at all visits, ≥25 at one or more visits and <30 at all visits, ≥30 at all visits. b. Use similar approach to determine BMI in late-life up until last available visit and determine change from mid-life. An alternative approach is to create BMI trajectories from V1-last observed visit.
7. Alcohol use a. Mid-life b. Change from mid- to late-life	Never, former, current (drinks per week available among current drinkers)	X	X	X	X	X	X	X	a. Using V1-V4: categorize participants as never drinkers, former drinkers before midlife, former moderate drinker in midlife (≤7 drinks/week for women, ≤14 drinks/week for men, does not drink at V4), former heavy drinkers (>8 drinks/week for women, >15 drinks/week for men, does not drink at V4), current moderate drinker at V4, current heavy drinker at V4. Collapse as needed. b. Use similar approach to define late-life alcohol use up until last available visit and then determine change from mid-life.
8. Smoking a. Mid-life Change from mid- to late-life	Never, former, current (pack-years can also be calculated)	X	X	X	X	X	X	X	a. Use Visits 1-4 to determine never, former, current smoker in mid-life (essentially, final value from Visit 4). b. Use similar approach to define late-life smoking up until last available visit and then determine change.
9. Physical activity a. Mid-life b. Change from mid- to late-life	Baecke index (eg, meeting PA guideline recs or ideal/ intermediate/poor based on AHA Life's Simple 7)	X		X		X	X		a. Average V2 & V4 to determine mid-life PA level. b. Average V5 & V6 (if available) to determine late-

									life PA levels and difference from mid-life.
10. Dietary intake	Semi-quantitative FFQ (eg, DASH, HEI or Med diet score)	X		X					Average intakes from V1 & V3 to define midlife dietary scores. Consider using DASH diet score.
Psychosocial factors									
11. Perceived social support	Interpersonal Support Evaluation List		X						Consider quartiles as there are no established cut points (See prior ARIC publications: 10.1093/ageing/afw060 and https://www.ahajournals.org/doi/full/10.1161/STROKEAHA.114.005815)
12. Social network	Lubben Social Network Scale		X						0-50 score categorized as: socially isolated (≤20), high risk for isolation (21–25), moderate risk for isolation (26–30) and low risk for isolation (≥31) (See prior ARIC publications: 10.1093/ageing/afw060 and https://www.ahajournals.org/doi/full/10.1161/STROKEAHA.114.005815)
13. Anger reactions	Spielberger Trait Anger Scale		X		X				Use average scores from V2 & V4; categorize as low, medium, high based on the literature (https://www.ahajournals.org/doi/full/10.1161/hs0102.101625)

*Time-fixed variables.

Outcomes

Functional status: Assessed based on participant's Short Physical Performance Battery (SPPB) measurement from their last available visit (i.e., concurrent with last available blood pressure in Visits 5-7). SPPB is a composite score based on performance of three tasks: balance, usual gait speed over four meters, and time to rise from a seated position five times without using their arms, each scored from 0-4 for a range of total scores from 0-12. Low physical function will be defined as an SPPB 0-6.[8] We will also consider defining the outcome as an SPPB score <10 (low or fair physical function).[8]

Dementia: We will use a previously described algorithm to determine dementia status and timing of onset based on Ascertain Dementia-8 informant questionnaires, Six-Item Screener telephone assessments, hospital discharge and death certificate codes, and Visit 6 and 7 neurocognitive evaluations.[11]

Cardiovascular disease: We will use a composite of coronary heart disease, stroke, or heart failure. Individual components of the composite outcome may be examined in supplemental analyses.

Analysis

In Aim 1, we will estimate the proportion of participants in our study population that maintain normal blood pressure from mid- to late-late, that have normal blood pressure in mid-life but not late-life, and that do not maintain normal blood pressure in mid-life. Additionally, we will determine the proportion who maintain normal blood pressure from mid- to late-life among the overall ARIC cohort, including those who were censored before age 75.

In Aim 2, we will include participants who maintain normal blood pressure through mid-life and examine the distribution of participant characteristics among those who do and do not maintain normal blood pressure in late-life. We will then examine characteristics which are associated with maintenance of normal blood pressure from mid- to late life by calculating risk ratios for maintaining normal blood pressure through mid- and late-life compared to maintaining normal blood pressure through mid-life but not late-life. We will use Poisson regression with robust variance estimates to calculate prevalence ratios controlling for other participant characteristics. The models we propose are as follows:

- *Model 1:* Adjusted for age, sex, race, and education
- *Model 2:* Additionally adjusted for mid-life health behaviors and psychosocial factors
- *Model 3:* Additionally adjusted for change from mid- to late-life in BMI, smoking, alcohol use, and physical activity

In Aim 3, we will examine physical function at each participant's last study visit and compare the proportion of those with low physical function status in each blood pressure maintenance category. We will then estimate the relative risk of low functional status by blood pressure maintenance categories, comparing those with normal blood pressure in mid- and late-life and those with normal blood pressure in mid-life but not late-life to those who did not have normal blood pressure in mid-life, and comparing those who maintain normal blood pressure from mid- to late-life to those with normal blood pressure in mid-life but not late-life. We will examine these associations controlling for other participant characteristics. The models we propose are as follows:

- *Model 1:* Adjusted for age, sex, race, and education
- *Model 2:* Additionally adjusted for mid-life health behaviors and psychosocial factors
- *Model 3:* Additionally adjusted for change from mid- to late-life in BMI, smoking, alcohol use, and physical activity

We will also examine associations with dementia and CVD in late life. For these analyses, we will include all participants who are alive at ARIC Visit 5, or Visit 6 if they do not attend Visit 5, who do not have a history of dementia or CVD when studying each respective outcome, at or

before Visit 5. We will follow them for the incidence of dementia and CVD. We will categorize their blood pressure in mid-life as normal or not. We will use time-updated blood pressure categories (maintained normal blood pressure yes/no) at study visits in late-life. Blood pressure categories will be treated such that once a participant develops elevated blood pressure or hypertension, their blood pressure category cannot return to maintaining normal blood pressure. We will use Cox proportional hazard models to examine the associations of maintaining normal blood pressure with CVD, controlling for other participant characteristics. The models we propose for each outcome are as follows:

- *Model 1:* Adjusted for age, sex, race, education (analyses of incident dementia will also include adjustment for APOEe4 status)
- *Model 2:* Additionally adjusted for all mid-life health behaviors and psychosocial factors
- *Model 3:* Additionally adjusted for time-updated BMI, smoking, alcohol use, and physical activity in late-life

In sensitivity analyses, we will examine the hazard ratios for dementia and CVD incorporating inverse probability weights to account for the potential effects of censoring (e.g., due to drop out or death) before Visit 5.[11]

For each aim, we will consider sensitivity analyses using other definitions of maintaining normal blood pressure based on pretreatment blood pressure and the slope of the change in systolic blood pressure over time.

Potential challenges and solutions

In Aims 2 and 3, participants may have missing data for characteristics of interest. We will consider using approaches such as multiple imputation in order to retain participants in the analysis.

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"? __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/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)?

MP #3810: Association of normal systolic blood pressure with specific cardiovascular disease outcomes and chronic kidney disease among healthy adults (Whelton S, et al)

MP #3543: Associations Between Mid-life Vascular Risk Factors and Late-life Physical Function Decline in the Atherosclerosis Risk in Communities (ARIC) Study (Skow, et al)

MP #3051: The association of middle and late-life blood pressure with conversion to MCI and dementia: The ARIC Study (Walker, et al)

MP #2394: Determinants of blood pressure trajectories from midlife to older age: the Atherosclerosis Risk in Communities (ARIC) Study (Balakrishnan, et al)

MP #2146: Systolic blood pressure trajectories and incident cardiovascular disease (Kucharska-Newton, et al)

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.

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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