ARIC Manuscript Proposal #2829

PC Reviewed: 09/13/16	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Associations of orthostatic hypotension and postural change in blood pressure with 20-year cognitive decline, incident dementia, and incident stroke: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): OH and cognitive outcomes

2. Writing Group:
Writing group members: Andreea M Rawlings; Stephen Juraschek; Gerardo Heiss; Tim Hughes; Michelle Meyer; Elizabeth Selvin; A Richey Sharrett; B Gwen Windham; Rebecca F Gottesman; others welcome

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

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3. Timeline: All data is currently available, we plan to submit for publication within 12 months of approval of the manuscript proposal.

4. Rationale:

Consensus definition of orthostatic hypotension (OH)[1,2] is a drop in systolic blood pressure (BP) of at least 20 mmHg and/or a drop in diastolic blood pressure of at least 10 mmHg within 3 minutes of standing. The prevalence of OH has been estimated between 5-35%, varying by population age and various comorbidities[3]. OH has been associated with incident cardiovascular disease and all-cause mortality, stroke, and syncope[4–8], but few have examined long-term associations with cognitive decline and dementia.

Studies to date have reported no association between OH and cognitive decline when OH was examined in older adults (mean age 72-80)[9–11]. Previously published results from ARIC[12] also found no association with cognitive decline over 6 years of follow-up in a middle-age population. Associations of OH with incident cardiovascular outcomes seem to depend in part on the age at which OH was ascertained, with stronger associations reported in populations <65 years old[4], potentially explaining the lack of association observed between OH and cognitive function in older adults.

There are three general hypotheses regarding a potential relationship between OH and cognitive function, including a shared pathological process that affects both, the hypothesis that cognitive impairment is a transient symptom of OH rather than a factor leading to long-term decline, and that OH is associated with persisting cerebral hypoperfusion and negatively impacts long-term cognitive funciton[13]. ARIC is ideally suited to investigate these aspects since OH, sitting blood pressure, and use of hypertension medications were assessed in midlife, there was comprehensive assessment of potential confounders, and over 20 years of follow-up allow for estimates of associations with long-term outcomes.

Our aim is to characterize the association of orthostatic hypotension and postural change in BP measured in midlife with 20-year cognitive decline and incident dementia. We also update previously published associations of incident stroke[7] with an additional 15 years of follow-up.

5. Main Hypothesis/Study Questions:

Our aim is to examine the association between OH and postural changes in BP measured at visit 1 and three cognitive outcomes:

a. 20-year cognitive decline (using measures at visit 2, 4, and 5)
b. Incident dementia (using hospitalization and visit-based assessment)
c. Incident stroke (using cohort surveillance from visit 1)

Hypothesis:

- OH and postural fall in BP measured at visit 1 will be associated with greater cognitive decline over 20 years, higher risk of incident dementia, and higher risk of stroke.

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

Prospective analyses. OH and postural change in BP assessed at visit 1

Exclusions

We will exclude participants who meet any of the following criteria:

- Did not undergo OH assessment at visit 1
- Race other than black or white, and blacks in Minneapolis or Washington County centers
- Missing covariates (described below)
- Persons with Parkinson's Disease (PD) and/or those taking medications used in the treatment of PD at visit 1

For analyses of 20-year cognitive decline, we will also exclude:

- Participants who did not attend visit 2 or who are missing cognitive assessment at visit 2

Part analyses of incident stroke, we will also exclude:

- Participants with a history of stroke or CHD at visit 1

Exposure – Orthostatic hypotension and postural change in blood pressure

Postural blood pressure was assessed using up to five measurements after changing positions from supine to standing. While the first measurement is often excluded from analyses, work in ARIC by Juraschek et al (MP#2611) has found the first measurement is generally more predictive of long term outcomes compared to later measurements. As a result, we will examine OH and postural change in blood pressure in a few ways:

- OH (yes/no): using consensus definition of a decrease in systolic blood pressure ≥20 mmHg or a decrease in diastolic blood pressure ≥10 mmHg upon standing. We will use both the first measurement only and the average of measurements to define change
- Change in postural blood pressure (continuous): We will examine change continuously (using linear and cubic splines and per SD to enable comparisons between SBP and DBP changes) and categorically (eg tertitles, quartiles, or groups of 5-10 mmHg) using the first and the average of measurements

Outcomes – 20-year cognitive change, incident dementia, incident stroke

20-year change:

Cognitive function was assessed in all participants at visits 2, 4, and 5 using the following standardized tests:

- Delayed word recall test (DWRT)
- Digit symbol substitution test (DSST)
- Word fluency test (WFT)

For each test, we will calculate a Z score by subtracting the test mean and dividing by the standard deviation. We will also create a global measure of cognitive performance by averaging the Z scores the three tests.

Incident dementia:

We will examine the coordinating center-created definitions of dementia (levels 1,2, and 3), with level 3 as primary.

- Level 1: Classification of dementia based on reviewer diagnosis and algorithmic syndromic diagnosis (based on visit 5 and prior visit information). Level 1 is only available for participants who came to visit 5 and underwent cognitive testing (categorized 0/1 for 6488 participants)
- Level 2: Classification of dementia based on reviewer diagnosis and algorithmic syndromic diagnosis (based on visit 5 and prior visit information), the telephone interview for cognitive status, and proxy interview (categorized 0/1 for 8777 participants)
- Level 3: Classification of dementia based on reviewer diagnosis and algorithmic syndromic diagnosis (based on visit 5 and prior visit information), the telephone interview for cognitive status, proxy interview, dementia codes on the cohort eligibility forms from hospitalizations, and dementia codes on the death certificate (categorized 0/1 for 15792 participants)

Incident stroke:

Stroke was ascertained via cohort surveillance of hospitalizations, annual telephone calls with participants or their proxy, and death certificates. Incident stroke will be defined as the first occurrence of definite/probable adjudicated hospitalization or ischemic stroke death. Surveillance data is available through the end of 2013, updating previously published associations[7] with an additional 17 years of follow-up.

Covariates

We will evaluate the following variables as confounders: age, sex, race-center, body mass index, education, diabetes, diabetes medication, diabetes duration, hypertension, hypertension medication use, apoE genotype, smoking, alcohol use, and physical activity.

Statistical Analysis

We will characterize our analytic population using means (standard deviations) or N (%) for all covariates.

We will analyze the relationship between the exposure variables and the following statistical models:

Model 1: Crude/unadjusted
Model 2: Model 1 + demographic variables (age, sex, race/field center, education)
Model 3: Model 2 + CVD risk factors (body mass index, hypertension, hypertension medication use, apoE genotype, diabetes, diabetes medication, smoking, alcohol use, physical activity)

20-year change:
We will model the associations using mixed-effects models, which account for the correlations between repeated measures of persons over time. We will include a random intercept, random slope for time (modeled using spline terms with a knot at six years, the median time between visit 2 and 4), and will assume that the random effects are independent.

Incident dementia:
We will use Cox proportional hazards regression for level 3 defined dementia. Follow-up will begin at the time of Visit 1 and will continue to incident dementia hospitalization, dropout, death, or the administrative censoring date December 31, 2013. We will test the non-proportional hazards assumption using log(-log) plots and testing risk-factor-by-time interactions. We will examine alternatives to Cox regression (described below) to account for the clustering of dementia cases around visit 5.

Incident stroke:
We will use Cox proportional hazards regression. Follow-up will begin at the time of Visit 1 and will continue to incident stroke hospitalization, dropout, death, or the administrative censoring date December 31, 2013. We will test the non-proportional hazards assumption using log(-log) plots and testing risk-factor-by-time interactions.

Effect Modification
We will examine possible effect modification by race, diabetes, hypertension, age, and sex.

Sensitivity analyses
We will consider the following sensitivity analyses:

- For analysis of 20-year change:
    - Participants who do not attend follow-up visits are likely informatively different from those who do, and may lead to biased estimated associations between the risk factors and cognitive function. To account for dropout, we will use multiple imputation by chained equations (MICE) to impute cognitive scores and missing covariates for persons who do not attend follow-up visits.
    - To mitigate possible floor effects, we will exclude participants scoring in the bottom 5-10th percentile of cognitive scores at baseline (we note this analysis may produce biased results in some cases and will analyze accordingly).
    - To determine potential mediating effects by stroke, we will censor participants who have a stroke after visit 2
- For analysis of incident dementia:
    - We will also define "incident dementia" using only hospitalization with an ICD-9 code of dementia, and will examine Level 1 and 2 coordinating center variables (described above)
    - Because of the clustering of dementia diagnoses around visit 5, we will also consider discrete time alternatives to Cox regression.

- As a way to assess ascertainment bias, we will censor individuals with hospitalizations commonly associated with OH, including syncope, falls, and/or dizziness that occur prior to (or at the same time as) a hospitalization with a dementia code

Challenges/Limitations

- Single time-point measurement of postural change in blood pressure may not reflect the individual's usual blood pressure response to postural change
- Dementia ascertainment will be clustered (i.e. most cases will be diagnosed around visit 5)
- We may have limited power in some subgroup analyses
- In analyses of 20-year change, differential dropout may lead to biased estimates
- We will not be able to rule out the possibility of residual confounding

7.a. Will the data be used for non-CVD analysis in this manuscript? x **Yes** _ **No**

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? _x **Yes** _ **No**
(This file ICTDER03 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 file ICTDER03 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/search.php
__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 #768: Postural Blood Pressure Change and Incident Stroke, Coronary Heart Disease, and All-cause Mortality (Eigenbrodt)
MP #1104: Orthostatic hypotension and cognitive function: the ARIC study (Rose)
MP #1560: Postural changes in blood pressure and incidence of ischemic stroke subtype in the ARIC study - Hiroshi Yatsuya

MP #2358: Association of posture-dependent changes in blood pressure with cerebral vascular lesions: the ARIC Neurocognitive Study (Poon)
MP #2611: Orthostatic Hypotension and Risk of Falls in the Atherosclerosis Risk in Communities Study (ARIC) (Juraschek)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? **__x__ Yes ____ No**

ARIC NCS

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 at http://www.cscc.unc.edu/aric/forms/

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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