ARIC Manuscript Proposal #3912

PC Reviewed: 8/10/21 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Association between middle age serum sodium and dementia risk: the Atherosclerosis Risk in Communities Study.

b. Abbreviated Title (Length 26 characters): Serum sodium and dementia

2. Writing Group:

Writing group members: Natalia I Dmitrieva (first author); Manfred Boehm; Mona Bahouth; Rebecca F Gottesman (senior author); others welcome

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

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

4. Rationale:

Our motivation for the current proposal to test the effect of overall hydration on cognitive decline and dementia came from our previous mouse studies and previous analysis of ARIC data obtained from the BioLINCC repository. In mice, we observed that life-long water restriction accelerated degenerative changes and shortened lifespan (Allen et al., 2019). These findings led to the hypothesis that chronic hypohydration in humans might accelerate age-related degenerative changes. Hydration status can be assessed by serum sodium because it is directly related to the water regulation cycle in the body and increases when we drink less fluid. Our previous preliminary analysis of ARIC data (through the BIOLINCC repository) showed increased prevalence of dementia at visit 5 among participants who had higher midlife serum sodium concentration (Allen *et al.*, 2019). To better understand factors underlying these findings, we propose to perform a comprehensive analysis of the associations between serum sodium, in midlife, as a measure of hydration habits, with long-term cognitive decline and dementia.

ARIC is ideally suited for the investigation of associations between hydration and cognitive decline because serum sodium was measured during midlife at visits 1 and 2, 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 serum sodium in midlife with cognitive decline and dementia.

For the current analysis, we propose to use serum sodium as a measure of life-long hydration habits- this decision may feel counterintuitive and require explanation. It is natural to think that hydration and serum sodium should change day to day depending on how much we drink on that particular day. But, surprisingly, clinical records demonstrate that for each particular person serum sodium concentration remains within a narrow range for 10 years (Zhang et al., 2014). Consistently, our previous analysis of sodium measurements performed during visits 1 and 2 in ARIC study demonstrated that serum sodium stayed within a very narrow range for each study participant (Gao et al., 2017). The reason for such stability is not completely understood but it is very likely that for the vast majority of people it is related to the amount of fluids they habitually consume on a regular basis. Differences between people could originate from varying drinking habits due to family traditions or different thirst perceptions that could be related to genetics. This assumption is supported by the large variations in fluid consumption reported in surveys performed across multiple countries worldwide. These surveys report that the average amount of fluids consumed by different people on a regular basis varies from 0.7L to 3-4L per day (Ferreira-Pêgo et al., 2015), indicating a large prevalence of hypohydration in general population.

Potential application for prevention: if a significant association of midlife serum sodium with cognitive decline and dementia is found, it would potentially indicate that maintaining good hydration may delay cognitive decline and dementia.

5. Main Hypothesis/Study Questions:

Our aim is to examine the association between serum sodium measured at visits 1 and 2 and three cognitive outcomes:

- 20-year cognitive decline (using measures at visit 2, 4 and 5)
- Incident dementia (level 3 definition)

Hypothesis:

Serum sodium at visits 1 and 2 will be associated with greater cognitive decline over 20 years and higher risk of dementia.

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. Serum sodium assessed at visits 1 and 2 vs cognitive decline and dementia diagnosis

Exclusions

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

- Did not have any serum sodium measurements available. Serum sodium was measured at visits 1 and 2. We will only exclude people who miss both these measurements. If only one visit is available then we will use that measurement. The reason for this choice is that sodium levels stay relatively stable in an individual, fluctuating around a level characteristic of every person depending on hydration habits. Therefore, averaging two measurements would give more accurate estimation of that level.
- Glucose level >140 mg/dl at whichever visits (1 or 2) serum sodium is taken from. The reason for this exclusion is that hyperglycemia results in an artificial decrease of measured serum sodium concentration (https://www.mdcalc.com/sodium-correction-hyperglycemia). Such dependency on glucose makes serum sodium measurements in these individuals inaccurate and therefore cannot be used as a measure of hydration status. This exclusion does not depend on fasting status, only on glucose concentration at the time of sodium measurement.
- Race other than black or white
- Non-Blacks from Jackson and non-whites from Washington County or Minnesota due to small numbers.
- Missing covariates
- For analyses of 20-year cognitive decline, we will also exclude: Participants who are missing cognitive assessment at visit 2
- Individuals with prevalent dementia at baseline (Visit 1)

Exposure – average serum sodium from visits 1 and 2 as a measure of hydration habits. If sodium measurement is available only for one visit then only one measurement will be used for these individuals.

We will also consider categories of serum sodium based on clinically meaningful or distribution-based cutoffs, and will evaluate for a nonlinear association with higher risk at lower sodium levels as well as high levels.

Outcomes –20-year cognitive change, incident dementia

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)

- 20-year cognitive change:

For each test, we will use ARIC-generated Z scores, calculated by subtracting the test mean and dividing by the standard deviation. We will also use the ARIC global measure of cognitive performance, calculated by averaging the Z scores of the three tests.

- Incident dementia:

We will use the coordinating center-created level 3 definition of dementia:

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

Covariates

We will evaluate the following variables as confounders: age, sex, race-center, body mass index, education, total cholesterol, glucose, eGFR, hypertension, hypertension medication use, heart failure, stroke, apoE genotype, smoking, alcohol use. The variables will be used from information collected at visit 1

Statistical Analysis

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

- 20-year cognitive 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. Methods will follow the recommendations of the ARIC-NCS Analysis manual.

- Incident dementia:

We will use Cox proportional hazards regression for level 3 defined dementia. Follow-up will begin at the time of Visit 2 and will continue to incident dementia hospitalization, dropout, death, or the administrative censoring date December 31, 2018. 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, 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).

- Challenges/Limitations
- All participants are requested to be fasting at the time of the study visits, and thus sodium levels may not necessarily reflect their status if not in a fasting state.
- Many factors/disorders affect serum sodium concentration in addition to hydration in lower end of physiological range (<136mmol/l) (Braun et al., 2015). This might lead to non-linear associations and require model adjustments in order to detect associations with dementia at higher sodium concentrations when hypohydration becomes a main cause of serum sodium increase.

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).

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)?

#2829 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 (Rawlings)

#3637 Associations of serum magnesium with cognitive function and dementia: The Atherosclerotic Risk in Communities Study (Alam)

#3239 Dietary patterns and risk of incident dementia and cognitive decline: Results from the ARIC study (Hu)

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 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.

References.

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