ARIC Manuscript Proposal #2501

PC Reviewed: 3/10/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:

Parathyroid hormone and subclinical cerebrovascular disease: an ARIC Brain MRI ancillary study

b. Abbreviated Title (Length 26 characters):

PTH and cerebral WMH

2. Writing Group:

Writing group members:

Erin D. Michos	Johns Hopkins	Lead Author	approved
Di Zhao	Johns Hopkins	Analyst	approved
Eliseo Guallar	Johns Hopkins		approved
Pamela L. Lutsey	University of Minnesota		approved
Alvaro Alonso	University of Minnesota		approved
A. Richey Sharrett	Johns Hopkins		approved
Wendy Post	Johns Hopkins		approved
Jared Reis	NHLBI		approved
Thomas Mosley	University of Mississippi		
Rebecca Gottesman	Johns Hopkins	Senior author	approved

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

Lead author: **Erin D. Michos, MD, MHS, FACC**

Address: Carnegie 568, Division of Cardiology, Johns Hopkins Hospital, 600 N. Wolfe Street, Baltimore, MD 21287

Phone: 410-502-6813 Fax: 410-502-0231
E-mail: edonnell@jhmi.edu

3. Timeline:

To start immediately

4. Rationale:

Elevated parathyroid hormone (PTH) levels may increase the risk for brain injury. Higher serum PTH concentration has been associated with incident hypertension,[1] impaired endothelial function, and increased aortic pulse pressure.[2] Elevated PTH levels have been associated with increased risk for cardiovascular disease (CVD) outcomes including subclinical vascular disease,[3] cardiovascular mortality,[4] sudden cardiac death,[5] and heart failure[6,7] in the general population. A 2013 meta-analysis found elevated PTH conferred a 45% excess risk for CVD events,[8] although a prior ARIC analysis did not find that elevated PTH to be an independent risk marker for incident CVD.

However, little data has examined the association of PTH levels with subclinical cerebrovascular disease. Elevated PTH has been associated with cognitive decline.[9] One only prior study was identified in the literature that evaluated PTH with white matter changes in the brain.[10] This was conducted in the Uppsala Longitudinal Study of Adult Men (ULSAM), a Caucasian population in Sweden, and found that PTH predicted both vascular dementia as well as white matter hyperintensities (WMH) on brain MRI. The brain MRI was performed 5 years after the PTH measurement, with no baseline brain MRI to examine white matter progression. Other limitations of that study are the inability to generalize to women or other race/ethnicities.

White matter hyperintensities and subclinical infarcts are commonly seen on brain MRIs of older adults.[11] Because of their wide variability in prevalence among older adults, their association with cardiac disease, prior stroke, and CVD risk factors, WMH are believed to be at least partially preventable through identification and treatment of modifiable risk factors. WMH, even in the absence of obvious neurologic deficits, are associated with reduced functioning on cognitive testing and subjective mental decline.[12]

Prior work by Mosley in the ARIC Brain ancillary study of 1949 individuals (aged 55-72) without a history of clinical stroke or TIA, found both high grade WMHs and silent infarcts were independently associated with lower scores on all the cognitive tests performed.[13] Thus, common subclinical changes seen by brain MRI are associated with reduced cognitive functioning in community-dwelling adults younger than 75 years. Furthermore, a subset (n=1134) underwent repeat brain MRI imaging 10 years later. Cumulative systolic blood pressure was found to be a strong predictor of WMH progression over follow-up.[14] Worsening MRI status, including incident subclinical infarction, progression of WMH and ventricular enlargement, was significantly associated with 14-year cognitive decline.

We previously examined the association of 25-hydroxyvitamin D [25(OH)D] with WMH prevalence, WMH progression, and incident infarcts in the ARIC Brain Ancillary Study.[15] Contrary to our hypothesis, we did not find any association of vitamin D with subclinical cerebrovascular disease. Further adjustment for PTH did not alter these findings. However, we did not directly examine the association of PTH with brain changes. Furthermore, the risk that PTH may confer on CVD and cerebrovascular disease may be through pathways independent of 25(OH)D. In the ULSAM study,[10] the association of PTH with WMH remained significant even after adjustment for 25(OH)D.

The prior study of PTH and WMH in the ULSAM study[10] did not include women or non-white race, which warrants trying to replicate their cross-sectional findings in the ARIC study. Furthermore, no prior study has evaluated the *prospective* association of PTH with white matter changes in the brain, as newly proposed for this paper.

5. Main Hypothesis/Study Questions:

1: To determine the cross-sectional association of PTH levels measured at visit 3 with the prevalence of white matter hyperintensities (WMH) and subclinical cerebral infarcts measured by Brain MRI at ARIC visit 3 (1993-1994).

2: To determine the *prospective* association of PTH levels at visit 3 with progression (worsening) of WMH and incident subclinical infarcts measured by repeat brain MRI performed 10 years later (2004-2006).

Hypothesis: Higher levels of PTH will be associated with increased subclinical cerebrovascular disease including prevalent WMH, greater WMH progression, and prevalent and incident subclinical infarcts independent of demographic and socioeconomic factors, vascular risk factors such as blood pressure and diabetes, and related biomarkers such as calcium, phosphate, and 25(OH)D.

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).

Participants: The ARIC Brain MRI ancillary study (R01 HL70825; PI Mosley) is a subset of ARIC participants age ≥55 years from the Forsyth County and Jackson sites that were invited for a cerebral MRI and cognitive testing during ARIC visit 3 (1993-1994) (n=1949, 60% women and 50% blacks). Inclusion/exclusion criteria for that ancillary study have previously been published. A subsequent ancillary grant (1R01NS072243-01; PI Michos) newly measured 25(OH)D, PTH, calcium, and phosphate levels from visit 3 stored blood from participants of ARIC Brain MRI ancillary study.

We will include participants who had PTH measured at visit 3 and with available brain MRI data. Participants who reported history of stroke at ARIC baseline or had an incident stroke prior to ARIC visit 3 will be excluded.

ARIC Study Timeline			ARIC Brain		ARIC Brain	ARIC-NCS
Exam	1	2	3	4		5
Calendar year	1987-1989	1990-1992	1993-1995	1996-1999	2004-2006	2011-2013
Follow-up year	0	3	6	9	17	24

Number, N	15792	14348	12887	11656	1134	7229
Age range, y	45-64	48-67	51-70	54-73	62-82	70-89
Vascular risk factors	X	X	X	X	X	X
Incident clinical events (i.e. stroke)	X	X	X	X	X	X
Cognitive Testing		X	X	X	X	X
Brain MRI, n			1959 (1878 free of stroke/TIA PTH		1134	2000 (547 with 2 prior brain MRIs)

Primary exposure: Parathyroid hormone measured at ARIC visit 3

Other covariates: age, sex, race, smoking, physical activity, education, BMI, systolic blood pressure, use of antihypertensive medications, total cholesterol, eGFR, serum calcium, phosphate and 25(OH)D. Will use visit 3 data when available. However, eGFR was assessed at visit 2.

Outcome ascertainment:
For the ARIC Brain MRI ancillary study, the cerebral MRI scanning protocol has been previously described.[13] At ARIC visit 3, WMH severity was qualitatively scored from barely detectable white matter change (Grade 1) to extensive confluent changes (Grade 8). The absence of WMH was scored Grade 0, and those with changes worse than Grade 8 were scored as Grade 9.

At the 2004-2006 second ARIC Brain visit, in addition to qualitatively scoring WMH by visual inspection into grades 0-9, a semiautomated quantitative volumetric analysis was performed as previously described. Using a quadratic fit, quantitative WMH volumes were found to be well-correlated with qualitative visual grade scoring (R^2=0.80).

Since quantitative WMH were not available for visit 3 scans, the ARIC Brain Ancillary Study investigators have imputed WMH volume scores for visit 3. The prediction equation was created using the actual data from the 2004-2006 ARIC Brain exam (where both visual grades and quantitative volumes were assessed on the same participants) and applied to the visual grades from visit 3 to estimate visit 3 volumes. Individuals who already had severe WMH on the first brain MRI (grade 7 or higher, n=2) were excluded as it is felt they would be unlikely to show progression, as well as 9 subjects with prior stroke. As previously published,[14,15] this provides 983 participants (49% black, 62% female, mean age of 72 years at the 2004-2006 visit) who completed 2 interpretable brain MRI scans. Of these, 4% of whites and 10% of blacks had WMH progression more than 2 grades. The average WMH change between the scans was 5.2 cm3 (median 2.7 cm^3, SD 8.6 cm^3).

At both ARIC brain visits, brain MRIs were also scored separately for subclinical infarcts by size and location.[15,16,17] Lacunes were defined as subcortical infarcts ≤20 mm in size. Incident infarcts were those seen on second brain MRI that were not present at visit 3.

[Repeat brain MRIs were performed again in the ARIC-NCS study (years 2011-2013), which includes ~500 survivors (now ≥70 years of age) who had 2 previous brain MRI scans. We will consider using this data as well, although factors related to attrition will need to be accounted for. Also the smaller sample size is problematic.]

Statistical analysis:

1. For each analysis, PTH levels will be analyzed both as a continuous variable per 1 SD increase as well as in categorized into quartiles (based on the overall population distribution) or dichotimized at clinical cutpoint of ≥65.

2. The cross-sectional association of PTH levels with WMH score (0-9) at visit 3 will be examined with both linear and non-linear regressions. To allow for non-linear relationship between PTH levels with WMH scores, we will model PTH levels using quartiles and using restricted cubic splines with knots at the 5th, 50th, and 95th percentiles. Tests for linear trend across quartiles will be conducted by including an ordinal variable with the median PTH level of each quartile in regression models The cross-sectional association of PTH levels with prevalent subclinical cerebral infarcts (>3 mm) and with high grade WMH (≥3) will be determined using multivariate logistic regression.

3. The prospective association between PTH levels with progression of WMH volume change will be analyzed first by categorizing PTH levels into quartiles. For more detailed dose-response analyses, we will model PTH using restricted cubic splines with knots at the 5th, 50th, and 95th percentiles of their sample distributions to provide a smooth yet flexible description of the relationship. The association of PTH levels with incident infarcts at the latter brain visit (excluding those with prevalent infarcts at visit 3) and with incident high WMH score ≥3 (excluding those with high score at visit 3) will be performed using multivariate logistic regression.

4. Regression models will include both limited covariate adjustment for age, race, gender and comprehensive multivariate adjustment including traditional CVD risk factors, lifestyle factors, and SES factors. Additional models will also include 25(OH)D, Calcium, Phosphate in the model to see if the association of PTH with cerebrovascular markers is still significant after taking into account these related biomarkers which could be mediators.

5. Interaction testing by race will be performed

6. We may also do sensitivity analyses accounting for attrition given only 58% of participants with brain MRI at visit 3 returned for 2nd brain MRI 10 years later.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ Yes ____ No

YES – looking at brain white matter changes, but this is felt to be related to CVD.

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? ____ 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? ____ Yes __X__ 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"? ____ 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)?

#2020 Michos "Vitamin D and subclinical cerebrovascular disease: an ARIC Brain MRI ancillary study"

#2184 Folsom: PTH and risk of CVD

#2222 Yao: PTH and incident HTN

#2486 Reis: PTH and incident diabetes

#1894: Hanff: Retinal abnormalities and white matter disease progression

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* 2010.01)
____ 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 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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