

ARIC Manuscript Proposal #2632

PC Reviewed: 9/8/15

Status: A

Priority: 2

SC Reviewed: _____

Status: _____

Priority: _____

1.a. Full Title: Parathyroid Hormone and Cognitive Change Over 20-years: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): PTH and Cognitive Function

2. Writing Group:

Writing group members:

Sai Krishna Korada	Northeast Ohio Medical University	First Author
Di Zhao	Johns Hopkins University	Second author, analyst
Pamela L. Lutsey	University of Minnesota	Third Author
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Erin D. Michos	Johns Hopkins University	Senior Author

[Note about the 5 proposed Hopkins authors: Erin Michos designed the concept and is the senior author. Di Zhao is the analyst. Eliseo Guallar is the mentor of Di Zhao and oversees the final statistical analyses. Rebecca Gottesman is part of the ARIC-NCS working group with cognitive expertise. Andrea Schneider has a similar proposal regarding vitamin D and 20-year cognitive change and was invited to ensure consistency of methods and avoid overlap.]

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

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3. Timeline:

Analyses to start immediately, goal to submit for publication within 6-12 months.

4. Rationale:

Elevated parathyroid hormone (PTH) levels have been associated with both cardiovascular disease (CVD) risk factors [such as hypertension, increased cardiac contractility, and release of vascular pro-inflammatory cytokines] and with CVD events in some cohorts.^{1,2,3,4,5,6,7,8} Elevated PTH may also affect brain health. The neuropsychiatric conditions associated with hyperparathyroidism may include lack of energy, stupor, and memory loss which can further be associated with dementia and mild cognitive impairment.⁹ PTH receptors are abundant throughout the brain and play an important role in neuronal calcium regulation, perfusion, and neuronal signaling.¹⁰ Elevated PTH has also been associated with a reduction in regional cerebral blood flow in primary hyperparathyroidism.¹¹

Additionally, PTH is intricately entwined in the regulation of serum vitamin D, calcium, and phosphate levels. PTH levels are elevated in the setting of 25-hydroxyvitamin D deficiency [25(OH)D], (i.e. secondary hyperparathyroidism). Vitamin D may be a neuroprotective steroid,^{12,13} and 25(OH)D deficiency has been correlated with an increased risk of Alzheimer's disease.¹⁴ Whether elevated PTH confers an increased risk of neurocognitive decline, independent of low 25(OH)D levels, is not well established.

Elevated PTH may be associated with cognitive decline;¹⁵ however, the literature is conflicting.¹⁰ In the Uppsala Longitudinal Study Of Adult Men (ULSAM) and Prospective Investigation Of The Vasculature In Uppsala Seniors (PIVUS) studies, elevated PTH was associated with vascular dementia and white matter hyperintensity (WMH) changes on brain MRI.¹⁶ . Recently, Lourida et al conducted a systematic review of PTH and cognition to assess the quality and findings from twenty-seven studies including a randomized controlled trial, several observational cross-sectional and case-control studies, and one prospective study.¹⁰ The authors found these studies to have low and moderate quality evidence and found mixed results that support a weak link between PTH, cognition and risk of dementia. Many of the studies identified in their review assessed the effect of surgery (parathyroidectomy) on cognition in participants with primary hyperparathyroidism. The systematic review by Lourida identified only one *prospective* study of PTH and cognitive decline. This study published by Björkman et al found that elevated PTH levels had two-fold risk of lower global cognitive function and all-type dementia over one and five year follow-up.¹⁰ Additionally, the systematic review by Lourida et al highlighted the fact that no studies adjusted for 25(OH)D and it was unclear if studies adjusted for ionized calcium.¹⁰

We previously examined the association of PTH levels measured during the ARIC visit 3 (1993-1995) with prevalence, WMH progression, and incident infarcts among 1,703 participants in the ARIC Brain Ancillary Study (**approved ARIC Proposal #2501, manuscript under ARIC review**). In cross-sectional analyses at visit 3, in models adjusted for demographic and lifestyle factors, we found that elevated PTH was associated with increased risk of prevalent infarcts and higher WMH scores. These findings were attenuated after accounting for other CVD risk factors and markers of mineral metabolism. Furthermore, we did not find that elevated PTH was independently associated with progression of cerebrovascular disease on brain MRIs obtained

approximately 10 years later. That study, however, was the first study looking at long-term brain MRI changes related to PTH and warrants further study of the relationship between PTH with subclinical cerebrovascular disease, cognitive function, and dementia.

Another ARIC study in progress is investigating the association of 25(OH)D and 3-epi-25(OH)D3 with cognitive function over 20-years follow-up (**approved ARIC Proposal #2357**) using visit 25(OH)D levels. This study has a large sample size (n~12,000) and also will evaluate possible modifying effects of race and genetic variations of vitamin D binding protein (VDBP). Our study will mirror this study in many aspects in terms of methods, however, we aim to examine the cross-sectional and prospective associations between PTH and cognitive function in this proposal.

In summary, there is currently uncertainty of the independent effects of elevated PTH with cognition, and the ARIC cohort is well suited to address this knowledge gap. We propose to investigate the association of PTH with both *cross-sectional* cognitive function measured at ARIC Visit 2 and *longitudinal* cognitive change measured over 20 years. Additionally, we propose to investigate possible mediating effects of biomarkers in the metabolic pathway, including calcium, phosphorus, and 25(OH)D. As blacks are known to have higher PTH levels and lower 25(OH)D levels than whites, we will also examine possible effect modification by race. In our previous work in ARIC, we have found that the association of 25(OH)D with CVD risk was stronger in whites compared to blacks. Furthermore, since Apolipoprotein E (APOE) ε4 is an established risk factor for cognitive decline and the development of dementia, we will also see whether the association of PTH with cognitive decline varies by APOE ε4 carriers.¹⁷

5. Main Hypothesis/Study Questions:

1. To determine whether elevated PTH levels at ARIC visit 2 are independently associated with *cross-sectional* cognitive performance assessed by the Delayed Word Recall Test (DWRT), the Digit Symbol Substitution Test (DSST), the Word Fluency Test (WFT), and a composite (global z-score) at ARIC Visit 2.

Hypothesis: Elevated PTH levels will be associated with lower global cognitive function, lower cognitive function on DSST and WFT (reflective primarily of vascular disease pathology) and on DWRT (test of memory, more reflective of Alzheimer's disease pathology) in the *cross-sectional* analysis of the participant cohort at ARIC Visit 2. This association will be independent of education level, CVD risk factors and markers of mineral metabolisms (i.e. vitamin D, calcium, phosphate).

2. To determine whether elevated PTH levels are independently associated with *prospective* cognitive change assessed by the Delayed Word Recall Test (DWRT), the Digit Symbol Substitution Test (DSST), the Word Fluency Test (WFT), and a composite global z-score) over 20 years of follow-up.

Hypothesis: Elevated PTH levels at ARIC visit 2 will be associated with global cognitive decline, cognitive decline on DSST and WFT (reflective primarily of vascular disease

pathology) and on DWRT (test of memory, more reflective of Alzheimer's disease pathology) in the *prospective* analysis of the participant cohort over 20 years of follow-up. This association will be independent of education level, CVD risk factors and markers of mineral metabolisms (i.e. vitamin D, calcium, phosphate).

3. To determine whether the association of elevated PTH with cognitive change differs by race and APOE ϵ 4 genotype.

Hypothesis: Associations of elevated PTH with cognitive change over 20-years of follow-up will be stronger among whites compared to blacks. Although APOE ϵ 4 carriers are at high risk for cognitive decline, we will not see a difference in association of PTH and cognitive decline between carriers and non-carriers.

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: Cross-sectional (ARIC Visit 2: 1990-1992) and prospective cohort study (baseline ARIC Visit 2: 1990-1992 through ARIC visit 5: 2011-2013).

Participants: All participants measured with cognitive and PTH data from ARIC Visit 2 except non-whites from Maryland or Minnesota, and those other than white or black race (n \approx 12,000).

We will exclude participants who self-reported a prior stroke at visit 1 or had an incident stroke before ARIC visit 2. We will exclude data from participants with the extreme outlier values of very low PTH (<10 pg/mL) or very high (\geq 200 pg/mL). We additionally will exclude data from individual study visits (not participants) when the individual reports taking CNS altering medications that may affect cognitive test performance.

PTH Variables: Blood samples were collected during each full cohort visit under careful conditions. Serum or plasma was separated at 4°C and promptly stored at -70°C. In 2012-2013, PTH, 25(OH)D, calcium, and phosphate were measured from stored serum obtained at ARIC study visit 2 (1990-1992). Serum PTH levels were measured using Elecsys 2010 (Roche Diagnostics, Indianapolis, Indiana). The inter-assay coefficients of variation (CV) was 7% for PTH.

Exposure: PTH levels, measured at visit 2, will be examined in several ways as has been done in prior ARIC analyses: (1) categorized into quartiles (based on the overall population distribution), (2) examined continuously per 1 SD of log(PTH) if association is found to be linear, and (3) dichotomized at clinical cutpoint of \geq 65 pg/ml (for elevated PTH).

We will also use examine the continuous distribution of PTH using restricted cubic splines with knots at the 5th, 50th, and 95th percentiles.

Covariates: (measured at ARIC visit 2, unless otherwise noted):

Demographic factors: age (continuous, centered), age² (continuous, centered), sex (male; female), and race/center (Minnesota whites; Maryland whites; North Carolina whites; North Carolina blacks; Mississippi blacks).

Socioeconomic and lifestyle factors: education (measured at visit 1, <high school; high school, GED, vocational school; college, graduate or professional school), smoking (never; former; current), alcohol consumption (current vs not current), physical activity by Baecke score¹⁸ (measured at visit 1, scored 1 to 5); body mass index (<25 kg/m²; 25-<30 kg/m², ≥30 kg/m²).

Cardiovascular disease related factors: systolic blood pressure (continuous), use of antihypertensive medications, diabetes (yes; no; defined as fasting glucose ≥126 mg/dl or non-fasting glucose ≥200 mg/dl or self-reported physician diagnosis or diabetes medication use); total cholesterol and HDL-cholesterol (continuous); prevalent coronary heart disease (yes; no; defined by standardized criteria and physician adjudication).

Outcome Ascertainments:

Cognitive function was assessed using the Delayed Word Recall Test (DWRT), the Digit Symbol Substitution Test (DSST), the Word Fluency Test (WFT), and a composite global z-score at ARIC Visits 2, 4, and 5.

The DWRT¹⁹ is a test of verbal learning and recent memory. Participants were given 10 common nouns that they were asked to learn by using each word in one or two sentences. After a five-minute delay, participants were given 60 seconds to recall the 10 words. The score is the number of words correctly recalled.

The DSST²⁰ is a test of executive function and processing speed. Participants were asked to translate numbers to symbols using a key. The score (range 0-93) is the total number of numbers correctly translated to symbols within 90-seconds.

The WFT²¹ is a test of executive function and language, and tests the ability to spontaneously generate words beginning with a particular letter, excluding proper names or places. Participants were given 60 seconds for each of the letters “F”, “A”, and “S”. The score is the total number of words generated across the three trials.

We will perform analyses using the raw cognitive test scores and using z-scores that were generated by the ARIC coordinating center for each cognitive test (at visits 2, 4, and 5), standardized using the visit 2 mean and standard deviation. We will also perform analyses using a global z-score. The coordinating center also averaged test z-scores to create global z-scores, which were then standardized using the visit 2 global z mean and standard deviation.

Statistical analysis:

All analyses will be performed in accordance with the ARIC-NCS analysis working group recommendations (details can be found in the ARIC-NCS analysis plan).

Linear regression models will be used to assess the cross-sectional associations of PTH with cognitive function at ARIC visit 2.

For the prospective analyses, briefly, we will use mixed-effects models with random intercepts and slopes for continuous outcomes to estimate the association between PTH and cognitive change over 20-years of follow-up. Time on study will be modeled using a linear spline with a knot at 6 years (approximately the time of visit 4). Our primary coefficients of interest will be the interaction of PTH with time spline terms.

We will examine the effects of attrition on our sample. Our prior work from the ARIC Brain MRI substudy found that those with elevated PTH had increased CVD risk factors and were less likely to return for follow-up study. We similarly anticipate that participants with higher PTH levels at visit 2 will be more likely to withdraw or die before ARIC Visit 5. Also those with cognitive decline are also more likely not to return. Thus, for the prospective analysis, we plan to account for this by using multiple imputation by chained equations (MICE) methods.²²

We will use progressively adjusted models as follows:

Model 1 will adjust for demographic variables: age, sex, race/center, and education level

Model 2 will also adjust for behavioral variables including education, body mass index, smoking status, alcohol, and physical activity

Model 3 will adjust for Model 2 and cardiovascular factors including systolic and diastolic blood pressure, use of hypertension medication, diabetes, HDL cholesterol, total cholesterol, cholesterol lowering medications, estimated glomerular filtration rate, and history of prevalent CHD.

Model 4 will adjust for Model 3 and biomarker mediators in the metabolic pathway including 25(OH)D (ng/ml), calcium (mg/dl), and phosphorus (mg/dl).

*Note that Model 2 will be our primary model, as vascular risk factors (included in Model 3) and related mineral metabolites (included in Model 4) actually may be mediators in the causal pathway between high PTH and cognitive decline, rather than confounding factors.

Modifiers: We will assess for age, sex, race and APOE ε4 genotype as effect modifiers.

Limitations/Challenges: The biggest limitation to this study will be attrition of participants. We plan to account for this by using multiple imputation by chained equations (MICE). Though this will not completely account for the effects of attrition, it will give us a more accurate estimate of the association between PTH and cognitive function.

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

Yes – Cognitive research, but we believe that this is directly related to the impact of CVD risk factors.

b. If Yes, is the author aware that the file ICTDER02 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 ICTDER02 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 No

We will assess differences by APOE4 genotype.

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 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.csc.unc.edu/ARIC/search.php>

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)?

#2501 (Michos): “Parathyroid hormone and subclinical cerebrovascular disease: an ARIC Brain MRI ancillary study.” This proposal evaluated PTH (measured at visit 3 in a subset from the ARIC Brain MRI ancillary study and looked at association of PTH with white matter changes in the brain. No cognitive analyses were examined in this proposal.

#2357 (Schneider) “Vitamin D, Vitamin D Binding Protein Genetic Polymorphisms, C-3 epimer Vitamin D3 and Cognitive Change Over 20-years: the Atherosclerosis Risk in Communities (ARIC) Study”. This proposal uses similar methods to look at vitamin D measured at ARIC visit 2 with cognitive decline. However the focus of our current proposal is PTH and cognition (not vitamin D and cognition). Furthermore Dr. Schneider was invited as a co-author to participate to ensure consistency of methods and avoid overlap.

2021 (Schneider), “Vitamin D and Cognitive Function and Dementia Risk in a Biracial Cohort: the ARIC Brain Ancillary Study”. This study examined vitamin D and cognitive decline in a subset (n=1700) from ARIC visit 3 through the ARIC Brain visit (10 year followup). PTH was adjusted for as a co-variate in a model, but the association of PTH with cognition was not addressed.

This proposal also is similar to other proposals that investigate associations between mid-life risk factors and cognitive change. We will work in accordance with the NCS analysis working group policies (i.e., before submission, we will circulate the manuscript to all listed on the “back-page” acknowledgments section). All analyses will be conducted in accordance with the recommendations set forth by the NCS working group.

#2160 - Diabetes and cognitive change over 20 years: the Atherosclerosis Risk in Communities Study (Rawlings)

#2175 - Midlife blood pressure and 20-year cognitive change: The ARIC-Neurocognitive Study (Gottesman)

#2284 - Lifetime socioeconomic position and cognitive decline: the ARIC-NCS study (Patel)

#2135 - Abnormal sleep characteristics and cognitive change: The Atherosclerosis Risk in Communities Study (Lutsey)

#2327 - Hearing impairment and cognitive performance in the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC NCS): cross-sectional and longitudinal results (Deal)

#1982 - Estimation of cognitive change from repeat measures in observational studies; associations with education: the ARIC NCS (Gottesman)

#2179 - Ischemic stroke risk score at baseline and 20-year cognitive decline: The Atherosclerosis Risk in Communities Study (Wruck)

#2245 - Lower extremity arterial disease and cognitive decline: the Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study (Palta)

#2201r - Lipids, stains, and 20-year cognitive change: The ARIC-Neurocognitive Study (Power)

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

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number* 2009.17, 2010.01)

B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____)

Lutsey ARIC Ancillary Study number

Michos ARIC Ancillary Study number

*ancillary studies are listed by number at <http://www.csc.unc.edu/aric/forms/>

12. 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.

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- ² van Ballegooijen AJ, Reinders I, Visser M, Brouwer IA. Parathyroid hormone and cardiovascular disease events: A systematic review and meta-analysis of prospective studies. *Am Heart J.* 2013 May;165(5):655-64, 664.
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