**ARIC Manuscript Proposal #2374**

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| **PC Reviewed: 6/10/14** | **Status: A** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: Serum fibroblast growth factor 23, phosphorus, 25-hydroxyvitamin D, parathyroid hormone and incidence of abdominal aortic aneurysm

**b. Abbreviated Title (Length 26 characters)**: FGF23, P, 25(OH)D, PTH & AAA

**2. Writing Group**:

Writing group members: Pamela L Lutsey, Aaron R Folsom, Lu Yao, Erin D. Michos, Alvaro Alonso, Weihong Tang. **Others are welcome.**

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


First author: Pamela L Lutsey
Address: 1300 South 2nd St, Suite 300
Minneapolis, MN 55126

Phone: (612) 624-5812 Fax: (612) 624-0315
E-mail: Lutsey@umn.edu


**ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).


Name: Weihong Tang
Address: 1300 South 2nd St, Suite 300
Minneapolis, MN 55126


**3. Timeline**: Data analyses will begin early summer. Goal completion by Oct 2014.

## 4. Rationale:

Abdominal aortic aneurysm (AAA) is a condition in which a portion of the aortic wall undergoes progressive dilation and weakening, potentially leading to aortic rupture if untreated[1]. In the United States in 2009 aortic aneurysms (of which most are abdominal) were the primary cause of 10,597 deaths and a contributing cause in more than 17,215 deaths[2].

Key features thought to underlie the pathogenesis of AAA are the progressive degradation and remodeling of elastin and collagen fibers of the aortic wall[3,4]. Relatively little is known about the etiology of AAA, though age, male sex, smoking status and hypertension are believed to be important risk factors. Serum concentrations of fibroblast

growth factor 23 (FGF-23), phosphorus, 25-hydroxyvtiamin D (vitamin D) and parathyroid hormone (PTH) – all biomarkers on the vitamin D metabolic pathway – may potentially contribute to AAA development. Although much interest in FGF-23 has related to its potential role in left ventricular hypertrophy[5], the coreceptor Klotho, which is mandatory to induce FGF-23 signaling pathways[6], is not expressed in the myocardium. It is, however, expressed in both human and rat aortas, as has been reviewed recently[6]. Additionally, in a rat experimental model of AAA, relative to controls those exposed to a FGF-23 antagonist had smaller aortic diameters and experienced a preservation of elastic fibers and smooth muscle cells[7]. FGF-23 has also been associated with endothelial dysfunction[8-10] and inflammation[11,12]. Phosphate excess, which is upstream to high FGF-23, has been associated with vascular calcification[13-15] and myocardial fibrosis[16].

If suboptimal vitamin D influences AAA risk, it likely does so predominantly by elevating established CVD risk factors which may also be associated with greater risk of AAA, namely hypertension[17-23] and inflammation[37, 38]. In a recent cross-sectional study which screened older men for AAA there was a dose-response relationship between low vitamin D and greater abdominal aortic diameter[24]. Higher PTH, which is downstream from low vitamin D, has been associated with impaired endothelial function, increased aortic pulse pressure, and decreased large artery elasticity[25].

To date, no epidemiologic studies have examined the association between FGF-23, phosphorus, vitamin D, PTH and incidence of AAA.

## 5. Main Hypothesis/Study Questions:

Serum concentrations of FGF-23, phosphorus, and PTH are associated positively with incidence of AAA, while serum vitamin D is associated inversely with AAA risk.

## 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).

Design: Prospective cohort from visit 2 (when biomarkers were measured) through the 2010 event follow-up for ARIC hospitalized AAAs, CMS through 2009 for CMS hospitalized and outpatient AAAs, and the abdominal aortic ultrasound exam at Visit 5. If AAA hospitalization and/or CMS events are updated, we will use the updated definition.

A time-to-event analysis will be used for hospital AAAs and CMS outpatient AAAs; a yes/no analysis will be used for the ultrasound data. Data will be pooled using meta-analysis techniques.

Outcome: All detected AAAs. ARIC does not have baseline data on AAA, so the presumption is that everyone is free of AAA at baseline and at risk for incident AAA.

Exposures: Visit 2 serum FGF-23, phosphorus, vitamin D, and PTH

Covariates: age, race, field center, sex, height, weight, smoking status and amount, diabetes, SBP and BP meds, TC, HDL, lipid meds, eGFR. Vitamin D and PTH will be adjusted for seasonality, as has been done in previous ARIC analyses.

Data analysis: Cox proportional hazards models for clinical/hospital AAA analysis and logistic regression for ultrasound AAA analysis.

The associations between baseline risk factors and AAA will be examined and reported separately for clinical and ultrasound-detected AAAs. For analyses on hospital AAAs, we will examine the proportionality assumption and use an appropriate form of Cox regression model to examine the association between baseline risk factors and subsequent clinical AAAs. For analyses on ultrasound-detected asymptomatic AAAs, we will exclude participants with known incident clinical AAA, and use logistic regression model to estimate the odds ratios for the associations, on the condition of fixed lengths of follow-up time. If a test of the homogeneity of associations for the two case groups is not rejected, results will be pooled using meta-analysis techniques and the pooled results will also be reported. All models will be adjusted for potential confounders.

Interactions will be tested by age, race, sex, smoking status, key vitamin D binding protein SNPs (i.e. rs7041 and rs4588; for vitamin D only) and eGFR (for FGF-23 only). Subgroup analyses will be reported, as appropriate.

**7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __X__ 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 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** (Interaction testing only; subgroup analyses if warranted)

**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)?**

**1505** Risk Factors for Abdominal Aortic Aneurysm (Tang)

**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* ___)**

2009.18 Tang AAA
2009.17 Lutsey Vit D

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

## References


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