ARIC Manuscript Proposal #2913

PC Reviewed: 12/13/16 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:
Prevalence and Risk Factors of Thyroid Dysfunction in Older Adults in the Community

b. Abbreviated Title (Length 26 characters): **Thyroid dysfunction in older adults**

2. Writing Group:
Writing group members: Nermin Diab, MD, CM; Natalie Daya, MPH; Stephen Juraschek, MD, PhD; Anna Kottgen, MD, MPH; Ulla T. Schultheiß, MD; Elizabeth Selvin PhD, MPH.

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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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).
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3. Timeline: All data are available. We anticipate a completing a draft of the manuscript within 6 months of MSP approval.

4. Rationale:

Background:
The prevalence of thyroid dysfunction varies by age, sex, race/ethnicity, and geographic factors [1,2]. The prevalence and treatment targets of thyroid dysfunction in the population are largely driven by middle-aged population studies. There is limited available data on the prevalence of thyroid dysfunction in the elderly population. Furthermore, some studies have shown that the TSH distribution shifts to higher values with increasing age, and hence guidelines for treatment of thyroid dysfunction might potentially be different for different age groups [2,3].

Moreover, prior studies have observed prevalence of thyroid dysfunction to be higher in persons with diabetes, but the link between thyroid dysfunction and diabetes is controversial [4,5]. In persons with diabetes, some studies have shown that thyroid disease adversely impacts glycemic control. However, our understanding of how thyroid dysfunction, particularly in asymptomatic subclinical thyroid disease patients, might affect glycemic control in persons with type 2 diabetes mellitus is unclear. Studying these associations may provide important information to inform diabetes care since there is little consensus on thyroid disease screening strategies in routine diabetes care [4].

Purpose of Study:
The primary purpose of this study is to investigate the prevalence of thyroid dysfunction in an older community-based population and to better understand possible sex and racial disparities within this age group. This study further aims to explore the relationship between thyroid dysfunction and its role in glycemic control in diabetic patients.

5. Main Hypothesis/Study Questions:

Study Questions:
Q1- What is the prevalence of thyroid dysfunction in an older community-based population?
Q2- Are there racial and sex differences in the burden of thyroid dysfunction in older adults?
Q3- Is there a higher burden of thyroid dysfunction in persons with diabetes and is thyroid dysfunction associated with glycemic control in diabetes patients?

Study Hypotheses:
Q1:

a) There will be a high burden of thyroid dysfunction, especially subclinical hypothyroidism in older persons in the community.

Q2:

a) African Americans will have a higher burden of thyroid dysfunction compared to whites
b) The prevalence of thyroid dysfunction will be greater in females compared to males and in persons with diabetes compared to those without diabetes

Q3:

a) In persons with diabetes, untreated hyper/hypothyroidism will be associated with poor glycemic control.

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 analysis

Inclusion/exclusion criteria
Inclusion Criteria:

- ARIC visit 5 (2011-2-013)
- n=6,538 participants
- all >65 years-old

Exclusion Criteria:

- Participants missing TSH/T3/FreeT4 lab test at ARIC 5 visit

Outcomes
All outcomes will be based on data collected during ARIC visit 5 which took place between 2011-2013. Participants received the same set of serum blood tests including but not limited to: Triiodothyronine (T3), Free thyroxine (FT4), Thyroid peroxidase antibody (TpoAB), Thyroid Stimulating Hormone TSH, Glycated Hemoglobin (HbA1c).

1) **Primary outcome:**
Prevalence of thyroid dysfunction stratified by age, sex, race and diabetes status. Thyroid dysfunction will be defined as any of the following:

- Clinical (overt) hyperthyroidism
- Clinical (overt) hypothyroidism
- Subclinical hyperthyroidism
- Subclinical hypothyroidism
- Treated hyperthyroidism
- Treated hypothyroidism

2) **Secondary outcome:**
Relationship between thyroid dysfunction and glycemic control in persons with diabetes.

Study variable definitions:
We will use the following definitions for each thyroid dysfunction category (main analyses will be conducted using ARIC defined cutoffs; we will conduct sensitivity analyses using race-specific cut-points and Roche-defined cut-points as has been done in previous ARIC papers):

Clinical (overt) Hyperthyroidism:

- Serum TSH < 0.56mlU/L and free T4 > 1.4 ng/dL

Clinical (overt) Hypothyroidism:

- Serum TSH >5.1 mlU/L and free T4 < 0.85ng/dL

Subclinical Hyperthyroidism:

- Normal free T4 (0.85-1.4ng/dL) and serum TSH below lower limit of reference range < 0.56mlU/L.

Subclinical Hypothyroidism:

- Normal free T4 (0.85-1.4ng/dL) and serum TSH higher than upper limit of reference range > 5.1mlU/L.

Treated hyperthyroidism:

- Self-reported hyperthyroidism diagnosis by a physician and taking hyperthyroidism (anti-thyroid) therapy: methimazole or propylthiouracil

Treated hypothyroidism:

- Self-reported hypothyroidism diagnosis by a physician and receiving hypothyroidism therapy: T3 supplements or T4 supplements or T3/T4 supplements

To address the relationship between thyroid dysfunction and diabetes, we will define diabetes as any of the following:

- Taking oral hypoglycemic therapy or insulin,
- Self-reported diabetes diagnosis by a physician,
- An HbA1c $\geq$ 6.5% or non-fasting glucose >200mg/dL or fasting glucose >126mg/dL.

We will conduct sensitivity analyses comparing associations in persons with diagnosed vs undiagnosed diabetes.

Other variables:

- TpoAb positivity will be considered for values > 34IU/ml
- Normal T3 levels will be defined as 90-168 ng/dL

Statistical Analysis

We will look at the prevalence of thyroid dysfunction as defined above overall and according to categories of age (65-70, 71-75,76-80, 80+), sex (male vs. female), race (white, African American), body mass index (normal weight, overweight, obese) and diabetes status (diabetic vs. non-diabetic).

We will use multivariable linear and logistic regression models to look at independent variables of interest including TSH, FT4, T3 levels, TpoAb levels (and positivity status) in the overall population and their associations with demographic and clinical factors. Adjustment variables will include demographics, body mass index, history of cardiovascular disease, physical activity, smoking habits and alcohol consumption. We will also adjust for clinical variables including the use of diabetes medications in participants with a history of diabetes.

We will also examine the association of thyroid parameters and definitions of thyroid dysfunction with glycemic control in persons with diagnosed diabetes. We will test for effect modification by age, sex, and race.

Anticipated methodological limitations

The cross-sectional design will limit our ability to draw conclusions about temporality and, as with any observational study, residual confounding will be a concern. Power may be limited for some analyses, especially for hyperthyroidism and population subgroups.

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? ____ 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? ____ 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)?

- The following are manuscripts published on thyroid dysfunction using the ARIC data:

1. Schultheiss, Ulla T., et al. "Thyroid function, reduced kidney function and incident chronic kidney disease in a community-based population: the Atherosclerosis Risk in Communities study." *Nephrology Dialysis Transplantation* (2016): gfw301.
2. Schultheiss, Ulla T., et al. "A genetic risk score for thyroid peroxidase antibodies associates with clinical thyroid disease in community-based populations." *The Journal of Clinical Endocrinology & Metabolism* 100.5 (2015): E799-E807.

- The following manuscript is under review:

Seth S. Martin, MD, MHS; Natalie Daya, MPH; Pamela L. Lutsey, PhD, MPH; Kunihiro Matsushita, MD, PhD; Anna Fretz, MHS; John W. McEvoy, MB BCh, MHS; Roger S. Blumenthal, MD; Josef Coresh, MD, PhD; Michael W. Steffes, MD, PhD; Philip Greenland, MD; Anna Kottgen, MD, MPH; Elizabeth Selvin, PhD, MPH
"Thyroid Function, Cardiovascular Risk Factors, and Incident Atherosclerotic Cardiovascular Disease: The Atherosclerosis Risk in Communities (ARIC) Study"

- The following are manuscript proposals related to thyroid dysfunction analysis using the ARIC data:

1. ARIC Manuscript Proposal #2489 - Subclinical Thyroid Dysfunction and Risk of Incident Fracture-Related Hospitalization; Anna Fretz; Natalie Daya; Seth Martin; Andrea L.C. Schneider; Casey Rebholz; John William (Bill) McEvoy; Michael Steffes; Pamela Lutsey; Anna Köttgen; Elizabeth Selvin

2. ARIC Manuscript Proposal #2492 - Thyroid Dysfunction, Cardiovascular Risk Factors, and Incident Events: The Atherosclerosis Risk in Communities (ARIC) Study; Seth S. Martin, Natalie Daya, Pamela Lutsey, Kunihiro Matsushita, Anna Fretz, John W. McEvoy, Roger S. Blumenthal, Josef Coresh, Michael Steffes, Phillip Greenland, Anna Kottgen, Elizabeth Selvin

3. ARIC Manuscript Proposal #2193 - Thyroid dysfunction and risk of chronic kidney disease ; Ulla T Schultheiss; Elizabeth Selvin; Morgan Grams; Michael Steffes; Josef Coresh; Anna Kottgen;

4. ARIC Manuscript Proposal #2151 - Thyroid dysfunction and venous thromboembolism; Aaron Folsom, Pam Lutsey, Saonli Basu, Susan Heckbert, Wayne Rosamond, Mary Cushman, Elizabeth Selvin

5. ARIC Manuscript Proposal #2781 - Thyroid function and atrial fibrillation: a Mendelian randomization study; ARIC Investigators: Alvaro Alonso, Dan Arking, Liz Selvin, Anna Kitten

6. ARIC Manuscript Proposal #2582 - The association between thyroid function and cardiac structure and function in older adults: the Atherosclerosis Risk in Communities (ARIC) Study. Georgina Gyarmati, Yuan Chen, John W. McEvoy, Seth Martin, Anna Köttgen, Amil Shah, Scott Solomon, Josef Coresh, Elizabeth Selvin, Kunihiro Matsushita

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* 2009.24 and _ 2009.16__)

___ 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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

References:

1) Bjoro, T., et al. "Prevalence of thyroid disease, thyroid dysfunction and thyroid peroxidase antibodies in a large, unselected population. The Health Study of Nord-Trondelag (HUNT)." *European Journal of Endocrinology* 143.5 (2000): 639-647.
2) Hollowell, Joseph G., et al. "Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III)." *The Journal of Clinical Endocrinology & Metabolism* 87.2 (2002): 489-499.
3) Vadiveloo, Thenmalar, et al. "Age-and gender-specific TSH reference intervals in people with no obvious thyroid disease in Tayside, Scotland: the Thyroid Epidemiology, Audit, and Research Study (TEARS)." *The Journal of Clinical Endocrinology & Metabolism* 98.3 (2013): 1147-1153.
4) Kadiyala, Raghu, R. Peter, and Onyebuchi E. Okosieme. "Thyroid dysfunction in patients with diabetes: clinical implications and screening strategies." *International journal of clinical practice* 64.8 (2010): 1130-1139.
5) Palma, Cátia Cristina Silva Sousa Vergara, et al. "Prevalence of thyroid dysfunction in patients with diabetes mellitus." *Diabetology & metabolic syndrome* 5.1 (2013): 1.