ARIC Manuscript Proposal #2489

PC Reviewed: 1/13/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Subclinical Thyroid Dysfunction and Risk of Incident Fracture-Related Hospitalization

b. Abbreviated Title (Length 26 characters): **Thyroid Dysfunction Fracture**

2. Writing Group:
Writing group members:

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

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3. Timeline: Data is currently available. Analysis is planned to start as soon as approval is obtained and will take between 3 and 6 months. Manuscript will be prepared during the 3 months following the completion of the analysis.

4. Rationale:

Thyroid dysfunction is a well-established risk factor for several cardiovascular (1, 2) and bone-related (3, 4) outcomes. Patients with overt thyroid dysfunction are usually symptomatic, readily diagnosed, and should be treated with anti-thyroid medication in the case of overt hyperthyroidism and thyroid hormone replacement therapy in the case of overt hypothyroidism (5, 6, 7). However, less is known about subclinical thyroid dysfunction and there is debate regarding whether to treat subclinical hyperthyroidism and subclinical hypothyroidism, defined as suppressed or elevated thyrotropin (TSH), respectively, in the context of reference range free thyroxine (T4) and triiodothyronine (T3) (8-10).

Subclinical thyroid dysfunction is fairly prevalent in the general population, with a prevalence of 5.0% among US adults who do not have a history of thyroid disease or prior thyroid medication use. Subclinical hypothyroidism is more common (4.3%) than subclinical hyperthyroidism (0.7%) (10). Subclinical thyroid dysfunction can be a result of endogenous or exogenous causes. In measuring subclinical thyroid dysfunction prevalence, it is important to distinguish between these two separate etiologies. As well, prevalence estimates vary by cut-point used.

The prevalence of endogenous subclinical hyperthyroidism is estimated to be 0.2% using the TSH cut-point < 0.1 mU/L from the National Health and Nutrition Examination. However, exogenous subclinical hyperthyroidism, namely due to thyroid-hormone replacement for hypothyroidism, is prevalent in roughly 9% of US adults (11), and thus contributes significantly to the overall prevalence of subclinical hyperthyroidism. Studies estimate that between 20-40% of individuals on thyroid hormone replacement therapy develop subclinical hyperthyroidism (12, 13). An overall estimate of subclinical hyperthyroidism, for both endogenous and exogenous causes, ranges from 0.7% to 2.2% in an adult population (11, 12). Although these two causes of subclinical hyperthyroidism (exogenous and endogenous) are different, their clinical effects appear to be very similar (14, 15). Endogenous subclinical hypothyroidism is prevalent in 3.9% of the adult population from NHANES III, while exogenous subclinical hypothyroidism is prevalent in 11% of those taking medication (11). Overall, subclinical hypothyroidism is prevalent in 4.3% to 9.5% of the US adult population (11, 12).

As there exists much debate over treatment guidelines for subclinical thyroid dysfunction, studies have measured follow-up TSH concentrations to assess progression of disease. A recent study found that after an average of 32-month follow up among those with subclinical hyperthyroidism at baseline, 56.7% of the patients remained subclinical, 11.8% progressed to overt hyperthyroidism, and 31.6% reverted to euthyroid level (16). Moreover, among patients with subclinical hypothyroidism at baseline, 28% progressed to overt hypothyroidism, while 68% remained subclinical and 4% reverted to euthyroid over 9.2 years of follow up (17). With the majority of patients remaining subclinical, this warrants the investigation of clinical outcomes associated with subclinical thyroid dysfunction.

The existing literature linking subclinical thyroid dysfunction to clinical risks is inconsistent. Several studies have reported associations between subclinical hyperthyroidism and incident cardiovascular outcomes and all-cause mortality (18-24). However, other studies have found no association for these various cardiovascular outcomes (22, 25-27), including 3 meta-analyses (28-30) as well as a major report (10). The literature has been somewhat conflicting for subclinical hypothyroidism, with some studies reporting an association with CVD and mortality (25, 31, 32), while others have not (22, 33, 34). However, a recent meta-analysis that extracted individual-level data from over 25,000 study participants demonstrates an association (35).

There are known effects of the thyroid hormones on bone and mineral metabolism, as shown in studies on patients with overt hyperthyroidism (3, 4, 36) and hypothyroidism (4, 36) as well as mechanistic papers assessing thyroid function and impact on bone mineralization (37, 38). Abnormal thyroid hormone levels, T3 and T4, in the setting of overt thyroid dysfunction, have a direct impact on bone metabolism. Elevated levels of thyroid hormones, T3 and T4, in the case of overt hyperthyroidism, accelerate bone resorption without compensatory bone formation, and thus reduce bone density (38, 39). Suppressed levels of T3 and T4, in the case of overt hypothyroidism, are not as well understood, however studies (4, 40, 41) have demonstrated that hypothyroid individuals have decreased bone resorption, with either normal or slightly increased bone mass (4). It is suggested that the apparent increased risk of fractures in hypothyroid individuals could be explained by reduced bone remodeling and renewal, or by confounding comorbidities, such as obesity, cardiovascular disease and neuromuscular complications that are associated with hypothyroidism and could lead to increased risk of fracture (4). Moreover, treatment of hypothyroidism with thyroid hormones increases bone resorption, causing reduced bone mineral density and increased risk of fracture (37, 38, 42).

However, much less is known regarding the possible clinical relevance of subclinical thyroid dysfunction on bone-related outcomes. Recent studies demonstrate the presence of TSH receptors in bone (39) and inhibitory effects of TSH on bone resorption (39, 43), which suggests that there may be a direct impact of TSH levels on bone metabolism. This offers plausibility to the association between subclinical thyroid dysfunction and bone mass. The current epidemiologic evidence linking subclinical thyroid dysfunction to risk of fracture is sparse and previous studies have been conflicting (44-51). Moreover, a recent meta-analysis concluded that the mixed results in the existing literature make it difficult to determine the association between subclinical hyperthyroidism and fractures, and that further longitudinal research is necessary (52). Better understanding the association of subclinical thyroid dysfunction and clinical outcomes could inform clinical guidelines for thyroid screening and treatment, which several studies have suggested as beneficial for cardiovascular outcomes (53-55) and bone-related outcomes for subclinical hyperthyroidism (36, 56), but not subclinical hypothyroidism (57-59).

Therefore, the primary aim of this study is to characterize the association between endogenous subclinical hyperthyroidism and incident fracture-related hospitalization in a community-based population. The secondary objective is to assess this same association in those with endogenous subclinical hypothyroidism. It is important to understand these individuals' risk of fracture, as persons with endogenous subclinical thyroid dysfunction would not be detected clinically. A sensitivity analysis will also be performed including those with exogenous subclinical thyroid dysfunction (due to treatment of either

hyperthyroidism or hypothyroidism), to evaluate if the risk of fracture is similar from over-treatment.

5. Main Hypothesis/Study Questions:

Aim 1. To evaluate the association between endogenous subclinical hyperthyroidism, defined as low TSH (<0.56 mU/L) with normal range free thyroxine (fT4),levels (0.85 ng/dL≤ fT4 ≤1.4 ng/dL), and incident fracture-related hospitalization.

> Hypothesis: Individuals with endogenous subclinical hyperthyroidism will have higher risk of incident fracture-related hospitalization than euthyroid individuals.

Aim 2. To evaluate the association between endogenous subclinical hypothyroidism, defined as elevated TSH (>5.1 mU/L) with normal range free thyroxine (fT4) levels (0.85 ng/dL≤ fT4 ≤1.4 ng/dL), and incident fracture-related hospitalization.

> Hypothesis: Individuals with endogenous subclinical hypothyroidism will have higher risk of incident fracture-related hospitalization than euthyroid individuals due to development of confounding risk factors that increase risk of fracture, such as obesity, neuromuscular symptoms, and cardiovascular disease.

Aim 3. To perform a cross-sectional analysis evaluating the association between subclinical thyroid dysfunction and several mineral metabolism markers: 25(OH)D, calcium, phosphate and parathyroid hormone

> Hypothesis: Individuals with subclinical thyroid dysfunction (both hyper- and hypo-) will have lower 25(OH)D levels, low calcium levels, high phosphate levels and high PTH levels compared euthyroid individuals.

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 cohort analysis of subclinical thyroid dysfunction and incident fracture-related hospitalization. Thyroid function tests were assessed at visit 2 which will serve as baseline for the present study.

Study Population (Inclusion/Exclusion Criteria):
All ARIC participants who attended visit 2 and who did not meet any of the following exclusion criteria:
-Identify as non-white race in Minnesota or Maryland
-The small number of persons who were neither black nor white
-Taking thyroid medication (anti-thyroid medication or thyroid replacement therapy) at visit 2
-History of hospitalized fracture prior to visit 2

Exposure:
Thyroid-stimulating hormone (TSH, thyrotropin) and free thyroxine (FT4) were measured in 2012-2013 at the University of Minnesota in stored serum samples originally collected from ARIC participants at visit 2 (1990-1992). For the main analyses, subclinical hyperthyroidism is defined from ARIC-derived cut-points: TSH <0.56 mU/L and 0.85 ng/dL ≤ FT4 ≤1.4 ng/dL, excluding participants on thyroid medication. Subclinical hypothyroidism is defined from ARIC-derived cut-points: TSH >5.1 mU/L and 0.85 ng/dL≤ FT4 ≤1.4 ng/dL, excluding participants on anti-thyroid treatment. In sensitivity analyses, we will examine the associations using cut-points provided by the manufacturer (Roche Diagnostics).

Laboratory Methods: Thyroid-stimulating hormone (TSH, thyrotropin)

Thyroid-stimulating hormone was measured in serum on a Roche Elecsys 2010 Analyzer (Roche Diagnostics Corporation) using a sandwich immunoassay method (Roche Diagnostics, Indianapolis). The lower and upper limits of detection were 0.005 mU/L and 1,000 mU/L, respectively. The inter-assay CVs from the University of Minnesota were 7.6% at a concentration of 0.195 mU/L and 4.5% at a concentration of 1.98 mU/L.

Laboratory Methods: Free Thyroxine (FT4)

Thyroxine (free) was measured in serum on a Roche Elecsys 2010 Analyzer (Roche Diagnostics Corporation) using a competition immunoassay method (Roche Diagnostics, Indianapolis). The lower and upper limits of detection were 0.023 mU/L and 7.77 mU/L, respectively. The inter-assay CVs from the University of Minnesota were 4.2% at a concentration of 1.22 ng/dL and 4.5% at a concentration of 2.84 ng/dL.

Outcome:
Fracture information was obtained from hospitalization data that was ascertained from annual telephone contact with study participants and through active surveillance of hospitalizations occurring in all study communities. ARIC hospitalization data are currently available through December 31, 2011. Incident fracture was defined using ICD9 discharge codes after visit 2 (1990-1992) of 733.1-733.19 (pathologic fractures), 733.93-733.98 (stress fracture), and 800-829 (fracture by injury). We categorized all diagnostic and procedural ICD-9 codes of each hospitalization using the Clinical Classification Software (CCS) developed by the Agency for Healthcare Quality and Research. The diagnostic ICD-9 codes for each hospitalization were classified into 18 systems-based categories and then sub-classified into 285 disease-based categories and the procedural ICD-9 codes were classified into 16 systems-based categories and then sub-classified into 231 disease-based categories (60).

Covariates:
Age (years, continuous), sex (male/female), race/field center (Maryland whites; Minnesota whites, North Carolina whites; North Carolina blacks; Mississippi blacks), education level (categorical), body mass index (continuous), smoking

(current/former/never), alcohol use (current/former/never), physical activity (categorical score), diabetes (yes/no), menopausal status in women (yes/no), 25(OH)D, calcium, phosphate, PTH, use of thyroid medications during follow up (thyroid hormones, anti-thyroid medications), and use of other medications related to fracture risk: anticoagulants (harmful), oral steroids (harmful), bisphosphonates (protective), thiazide diuretics (protective), statins (protective) estrogens (protective), beta-blockers (protective), vitamin D supplementation (protective).

Statistical Analysis:

We will use standard survival analysis methods and Cox proportional hazards models to evaluate the association of baseline subclinical thyroid dysfunction (vs euthyroid) with risk of incident fracture-related hospitalization. We will also employ Fine & Gray's competing risk method (61) to account for intervening deaths, giving the associations between subclinical thyroid dysfunction and mortality.

Sensitivity Analyses:

We will perform seven sensitivity analyses:

1. Sensitivity analysis evaluating the association between subclinical hyperthyroidism, including both endogenous and exogenous cases, and risk of fracture-related hospitalization and compare the strength of association to that observed for just endogenous subclinical hyperthyroidism (Aim 1).
2. Sensitivity analysis evaluating the association between subclinical hypothyroidism, including both endogenous and exogenous cases, and risk of fracture-related hospitalization and compare the strength of association to that observed for just endogenous subclinical hypothyroidism (Aim 2).
3. Sensitivity analysis comparing the strength of association between endogenous subclinical thyroid dysfunction and incident fracture using ARIC cut-points and the more specific Roche cut-points.
    a. Subclinical Hyperthyroidism: ARIC (TSH< 0.56 mU/L and 0.85ng/dL≤ FT4 ≤1.4 ng/dL) vs Roche (TSH<0.27 mU/L and 0.93 ng/dL ≤FT4≤1.7 ng/dL).
    b. Subclinical Hypothyroidism: ARIC (TSH>5.1 mU/L and 0.85ng/dL≤ FT4 ≤1.4 ng/dL) vs Roche (TSH>4.2 mU/L and 0.93 ng/dL ≤FT4≤1.7 ng/dL).
4. Sensitivity analysis using data only from North Carolina to assess race-field center aliasing.
5. Accounting for progression to overt thyroid dysfunction by excluding those who are identified as taking anti-thyroid medication or thyroid hormones during the follow-up visits.
6. Sensitivity analysis looking at pathologic fractures (ICD9 733.1-733.19) and stress fractures (ICD9 733.93 - 733.98; ICD9 800-829) as separate outcomes.
7. Sensitivity analysis assessing the associations between subclinical thyroid dysfunction and different fracture sites.

Potential effect modifiers:

We will test for interaction by age, race, sex and menopausal status (in women). A stratified analysis will be performed if statistically significant effect modification for any of the mediators is observed, using p-interaction < 0.10.

Limitations:
We are limited by the one set of thyroid measurements at visit 2, and thus cannot characterize the progression of subclinical thyroid dysfunction from visit 2, using TSH, free T4 and T3. However, we will conduct sensitivity analyses censoring those who use thyroid medication after visit 2 to account for incident treatment. The ascertainment of the outcome through ICD-9 codes will limit us to the most severe cases of fracture (inpatient hospitalizations only), however this is a highly specific outcome and it is these cases that result in greatest burden of morbidity and healthcare resources.Lastly, because this is an observational study only, we will not be able to rule out the potential for confounding.

7.a. Will the data be used for non-CVD analysis in this manuscript? _X_ Yes ____ 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?
____ 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)?

MS #1769: Diabetes, Glycemia, and Incident Fracture Risk: The Atherosclerosis Risk in Communities (ARIC) Study

MS #2151: Thyroid Dysfunction and Venous Thromboembolism

MS #2193: Thyroid Dysfunction and Risk of Chronic Kidney Disease

MS #2329: Ankle-Brachial Index and Long-Term Risk of Fractures: the Atherosclerosis Risk in Communities (ARIC) Study

MS #2371: Chronic Kidney and Risk of Fracture Hospitalization: the Atherosclerosis Risk in Communities Study

MS #2376: 25-Hydroxyvitamin D Levels, Vitamin D Binding Protein Gene Polymorphisms, and Vitamin D3 Epimer with Risk of Incident Fracture-Related Hospitalization: Twenty-Year Follow Up in a Bi-Ethnic Cohort

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

ARIC Ancillary Study #2009.24: Subclinical Thyroid Dysfunction and Clinical Outcomes (Selvin)

11.b. If yes, is the proposal

_X_ A. primarily the result of an ancillary study (list number* #2009.24)

___ 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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