Ancillary Study Proposal Form

Atherosclerosis Risk in Communities (ARIC)

I. Basic Study Information and Projected Impact on ARIC

1. Title of study**: Subclinical Thyroid Dysfunction and Clinical Outcomes (ARIC Thyroid Ancillary Study)**

2. Principal investigator(s) (name, address, phone and fax numbers, e-mail address):

Elizabeth Selvin, PhD, MPH
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3. Collaborators (must include at least one ARIC investigator):

Michael W. Steffes, MD, PhD (Laboratory)
Aaron Folsom, MD, MPH (University of Minnesota)
Josef Coresh, MD, PhD (Hopkins)
Paul Ladenson , MD (Hopkins)
David Cooper, MD (Hopkins)
Frederick Brancati, MD, MHS (Hopkins)
Phil Greenland (Northwestern University)
Ranee Chatterjee MD, MPH (Hopkins, General Internal Medicine Fellow)
Lisa Wyman (Hopkins, PhD Student)

Others welcome

We also welcome manuscript proposals from other investigators and anticipate the involvement of a number of other ARIC experts in specific laboratory or disease areas.

4. Summary of ARIC centers and tasks involved (NA=not applicable)

Center	Enroll or examine participants (N)	Assay samples (N participants)	Provide samples (N participants)	Analyze data (yes/no)
Forsyth Co. Field Center (Forsyth Co, North Carolina)		NA	NA	NA
Jackson Field Center (Jackson, Mississippi)		NA	NA	NA
Minnesota Field Center (Minneapolis, Minnesota)		NA	**Serum Visit 2 (N=14,166), Visit 5 (N=~9,373)**	NA

Washington Co. Field Center (Washington Co, Maryland)		NA	NA	**YES (Selvin)**
DNACentral Lab	NA			NA
Lipid Central Lab	NA		**Serum CARMRI (N=2,230)**	NA
Hemostasis Central Lab	NA			NA
ECG Reading Center	NA			NA
Coordinating Center (UNC)	NA			**Blind duplicate QC analyses only**

5. ARIC participant and staff involvement:

   A. Participants:
   Describe number of subjects needed; special characteristics of study population; age and sex distribution. Will participants be contacted, interviewed, or examined? If so, describe participant involvement. Estimate time required of each participant.

   <u>The Subclinical Thyroid Disease and Clinical Outcomes Study (ARIC Thyroid Ancillary)</u> will involve use of the stored serum specimens from all participants from Visit 2, all participants at the CARMRI visit, and all participants at the planned Visit 5.

   Estimated sample size*:
   Visit 2: N=14,166
   CARMRI Visit: N=2,230
   Visit 5: N=9,373

   *** All sample size estimates include a 3% sample of masked duplicate specimens.**

   We are proposing analyses of existing stored specimens only. There will be no additional contact with participants for this Ancillary Study.

B. Stored ARIC specimens:

Describe materials to be used (e.g., stored plasma, urine, DNA). If blood samples are requested, please review the Criteria for Approval section of the Ancillary Study Policy (http://www.cscc.unc.edu/aric/ancilary.htm) in consideration of your description of the following:

i. Study year(s) for which samples are to be used
Visit 2 (1990-1992), CARMRI Visit (2005-2006), and Visit 5 (2011-2013)

ii. Sample type (eg. Serum, EDTA, citrate, DNA)
Serum

iii. Requirement for frozen vs. previously thawed samples
Freeze-thaw is not thought to be a major concern for these analytes

iv. Sample volumes

	Sample Volume (uL)	CV(%)
TSH	50	<3%
Free-T4	15	<3%
Total T3	30	<10%
Anti-thyroid peroxidase Ab	10	<9%
Dead Volume	100	
Total Volume	**200**	

We anticipate that the Visit 2 measurements will be conducted along with a number of other measurements in coordination with Dr. Aaron Folsom and other investigators. Dead volume would typically require 200 uL for these measurements, but coordination with other proposals may eliminate the dead volume related to these tests. Specifically, for Visit 2 samples, these tests will be conducted by Dr. Steffes' laboratory on the same aliquot proposed for PTH measurement (Drs. Folsom and Lutsey's approved ancillary study of Vitamin D/PTH/calcium). We anticipate that storage vials will be compatible with the auto-analyzer. Thus, we anticipate that only incremental volume will be required for the Visit 2 measurements. Dead volume may apply to CARMRI and Visit 5 samples. If a sub-aliquot is needed, 200 uL will be used.

v. Efforts to integrate sample needs with those of other studies to conserve sample and/or limit freeze-thaw cycles.

These assays will be conducted on the Roche Elecsys 2010, a high-throughput multi-channel analyzer. Testing will be coordinated with other grants that have successfully obtained funding for measurement of serum analytes. We

will coordinate directly with Dr. Folsom and other investigators with funded proposals utilizing these samples.

C. ARIC Field Centers:
Describe effort (and estimated time) required of ARIC staff at each participating center.

Dr. Michael Steffes's laboratory at the University of Minnesota, will conduct all assays.

The investigators have previously worked with Dr. Steffes to measure HbA1c in all ARIC Visit 2 long-term stored whole blood specimens (N=14,069), measurements of glycemic markers in serum from CARMRI (N=2,033), and Drs. Selvin and Folsom have recently submitted grants to measure glycemic markers and Vitamin D, PTH, calcium and other analytes in collaboration with Dr. Steffes in the Visit 2 specimens.

Dr. Steffes is a world expert in the measurement and standardization of HbA1c. For more than 20 years, this laboratory has been the Central Biochemistry Laboratory for the DCCT and EDIC studies, with documented overall consistency (accuracy, stability, and precision) of HbA1c measurements and other assays, including renal function and lipids. In addition to ARIC and DCCT/EDIC, this laboratory has a strong track record of collaboration with large epidemiologic studies including NHANES, ALLHAT, FamilyHeart, PEACE, CORAL, CLEVER, MESA, and CARDIA.

D. ARIC Coordinating Center:
Describe effort (and estimated time) required of ARIC Coordinating Center staff. Specifically:

i. Will the Coordinating Center be involved in data collection, tracking, or preparation of forms or software? or Will these tasks be completed locally by the Ancillary Study, and a data file sent to the Coordinating Center?

All tracking and preparation of forms will be conducted locally by the Ancillary Study investigators at Johns Hopkins.

ii. If a Reading Center or laboratory is involved, will data be sent directly from the Reading Center or laboratory to the Coordinating Center for processing, or will processing be done locally (either by the Ancillary Study or at the Reading Center/Laboratory)?

N/A

iii. Will analyses be done locally by the Ancillary Study or by analysts at the Coordinating Center? If analyses will be done locally, should Coordinating Center verify the analyses?

All analysis will be conducted locally by the Ancillary Study investigators at Johns Hopkins. It will not be necessary for the Coordinating Center to verify the analyses. All resulting data will be provided promptly to the Coordinating Center according to ARIC policy.

iv. How many papers do you estimate will be written from the Ancillary Study?

We anticipate that 6-10 manuscripts will be written based primarily on the data generated by the proposed ancillary study. Additional collaborators will be invited for data analyses and writing groups of specific papers. We anticipate these data will be useful to other investigators immediately and in the future in studies involving markers of thyroid function.

6. Variables/measurements from the ARIC main study database to be analyzed:

<u>Major outcomes of interest</u>:

We are particularly interested in the association of subclinical thyroid dysfunction and the following clinical outcomes:

- **Incident cardiovascular disease and all-cause mortality**
- **Congestive heart failure**
- **Incident arrhythmias**
- **Changes in cognitive functioning (Visit 2 to Visit 4 to Visit 5) and dementia/MCI/neuro-cognitive status at Visit 5**
- **Depression (CES-D assessed at CARMRI and Visit 5)**
- **Changes in LDL-cholesterol and other cardiovascular risk factors**
- **Insulin resistance and incident diabetes (diabetes detected at Visits 2-4 and during annual follow-up telephone calls)**
- **Incident fracture (hospitalization)**

<u>Major covariates of interest</u>: Socio-demographic information (e.g. age, sex, race, center), anthropometric data (e.g. height, weight, body mass index, waist hip ratio), blood pressure, lipids (e.g. HDL, LDL, total cholesterol), chemistries (e.g. glucose, insulin), physical activity information, and interview data (e.g. family history of diabetes, family history of CHD, fasting status, self-reported health status, physical activity, social support, socioeconomic status), medication use.

<u>Future studies</u>: collaborations with other ARIC investigators to conduct GWAS of thyroid function markers

7. Genomic information (defined as any data from a participant's DNA):
   A. Does your proposal include any genomic materials? (please check one)
      _X_ No (go to question 8) ___ Yes (see question 7B)

   B. Name the gene(s), genotypes, SNPs to be investigated.

   C. Is genetic information used to address a primary aim or secondary aim of ARIC? (please check one or both)

      ____ Primary aim (heart/vascular disease)
      _ _ __ Secondary aim (other health conditions)
      List the conditions addressed:
      _____

   D. Should DNA-based results be reported to patients' physicians? Base your response on your knowledge of existing literature and current practice regarding increased risk and availability of treatment for adverse outcomes associated with the gene mutations to be studied.

8. Proposed starting and ending dates:

   We are in the process of preparing an R01 application for submission to NIH in February 2010 that will fund the proposed work.

   If funded, the proposed Visit 2 measurements will be conducted in collaboration with Dr. Folsom and will begin when funding is secured and in coordination with other planned measurements from these samples

9. Estimated cost by year; number of years:

Lab Test	Cost per Assay
TSH	$3.75
Free T4	$3.75
Total T3	$3.75
Anti-thyroid peroxidase Ab	$3.75

10. Source of funding; date of submission:

    We will submit an R01 in February 2010. The proposed research is responsive to a current program announcement from the NIA ("Thyroid in Aging (R01)"):
    http://grants.nih.gov/grants/guide/pa-files/PA-08-037.html

11. Does this study involve the support or collaboration of a for-profit corporation, or do you intend to use the data to patent any process, aspect or outcome of the analysis?

No. We do not intend to patent any process, aspect, or outcomes of this analysis.

12. What is the advantage, both to ARIC and yourself, of conducting the study within the ARIC cohort versus another population?

Advantages of conducting this study within ARIC are: (1) the availability of stored serum with comprehensive and rigorous measurements of clinical and subclinical outcomes; (2) large number of individuals with cardiovascular in a community-based population; relatively large numbers with clinical thyroid disease (8.9%) at Visit 3; (3) availability of extensive data on diabetes, metabolic measurements, cognitive function, and depression in addition to cardiovascular outcomes; (4) availability of the CES-D depression score administered in the CARMRI subsample; (5) the planned Visit 5 in which additional extensive information characterizing dementia and neuro-cognitive and physical functioning in the now elderly participants will be available; and (6) expertise and considerable experience of ARIC collaborators. The PI has previous experience working with ARIC investigators and ARIC data. We have completed two previous ARIC Ancillary Studies in which we measured HbA1c on all participants at the second ARIC examination and a number of other studies in progress.

We are specifically requesting CARMRI specimens to be able to examine the cross-sectional association between thyroid function and depression assessed by the CES-D instrument (CES-D data are not available at Visit 2) and the natural history of thyroid function across the life-course: from mid-life to old age. We will measure thyroid function at 3 points in time among the subsample of individuals alive at Visit 2, CARMRI, and Visit 5. These data will allow us to assess to characterize the trajectories of markers of thyroid function in a general population.

13. Impact on ongoing ARIC studies (main study or other Ancillary Studies):

This study will involve use of stored samples from Visit 2 in collaboration with ARIC Investigators. There will be no other anticipated impact on the main study or other Ancillary Studies. Results and measurements obtained in this Ancillary Study should be of interest to other ARIC investigators studying outcomes related to thyroid disease.

14. Provide the following assurances (answer each):

(1) Who (name and position) will report progress of the study in the fall of each year? (Ancillary Study PI or designate preferred)
PI: Elizabeth Selvin, PhD, MPH, Assistant Professor of Epidemiology & Medicine, lselvin@jhsph.edu

(2) How will confidentiality of ARIC participants be maintained?

The proposed study is based entirely on previously collected data and stored blood samples. There will be no contact with human subjects and the study does not pose any unusual risks to participants. Data collected in the ARIC Study, including laboratory samples, have been stripped of personal identifiers and investigators have signed and will adhere to requirements of the ARIC Data Distribution Agreement. Data collected in this ancillary study will be used by the investigators solely in connection with the outlined research study.

(3) Data collected by the Ancillary Study, with documentation (an archival copy of newly collected data with labels, and/or laboratory results as well as documentation on methods, visits and units used with specific instructions for using the data in analyses such as exclusions that were applied), will be provided to the ARIC Coordinating Center for integration into the main database. After that has been done the Ancillary Study investigators will receive the integrated file containing data from the main study. The Ancillary Study PI will be given the first and exclusive opportunity to analyze, present and publish data collected under the auspices of the Ancillary Study. After a reasonable time (in general, 12 months after data cleaning is complete or 12 months after acceptance of primary manuscript, whichever is earlier), Ancillary Study data will be made available for additional uses by other ARIC investigators. It is the responsibility of the Ancillary Study PI to state in writing to the ARIC Steering Committee any special circumstances that would warrant an exception to these guidelines for data sharing. In the spirit of encouraging collaboration, reasonable and justified requests for limiting Steering Committee access to the data will be honored, or some compromise will be worked out.
__ES__ We agree to these terms.

II. Abbreviated Ancillary Study Proposal

Purpose:
The association of subclinical thyroid dysfunction with adverse clinical outcomes including cardiovascular disease, cognitive decline, and depression is unclear. Because the existing data are conflicting, screening for subclinical thyroid dysfunction is controversial. The overarching objective of this proposal is to examine the clinical sequelae of subclinical thyroid dysfunction in the general population with a focus on cardiovascular disease and its risk factors, depressive symptoms and cognitive function.

> *We hypothesize that subclinical thyroid disorders are associated with the development and progression of subclinical and clinical cardiovascular disease and its risk factors, depression, and cognitive functioning in middle-aged and older adults.*

To achieve the following specific aims, we propose to measure thyroid stimulating hormone (TSH), free T4, total T3, and anti-thyroid peroxidase antibodies in stored serum from participants in the Atherosclerosis Risk in Communities (ARIC) Study—an NHLBI-funded community-based epidemiologic study of middle-aged black and white individuals followed for over two decades:

Specific Aims and Hypotheses:

Aim 1: To investigate the prospective association of subclinical thyroid dysfunction with changes in metabolic parameters and cardiovascular morbidity and mortality in a community-based population during two decades of follow-up.

> **Hypothesis 1.1:** Subclinical hypothyroidism is an independent risk factor for changes in LDL-cholesterol, body mass index, and measures of insulin resistance
>
> **Hypothesis 1.2:** Subclinical hypothyroidism is an independent risk factor for subclinical and clinical cardiovascular disease and all-cause mortality.
>
> **Hypothesis 1.3**: It will be possible to identify thresholds of TSH levels that identify individuals at high risk for the development of disease.

Aim 2: To investigate the association between hyperthyroidism and incident atrial fibrillation, stroke, and congestive heart failure

Aim 3: To investigate the associations between subclinical thyroid dysfunction, cognitive decline and depressive symptoms.

Aim 4: To investigate the association between hyperthyroidism and fracture risk (hospitalization)

Aim 5: To characterize the natural history and trajectory of thyroid functioning over the life-course from mid-life to old age.

Background:

Subclinical thyroid dysfunction and cardiovascular disease and cardiovascular risk factors

Subclinical hypothyroidism is a disorder defined by an elevated thyroid-stimulating hormone (TSH) level but normal levels of free thyroxine (free T4) hormone. This condition is estimated to affect approximately 4-8% of the US adult population with increasing prevalence in older age groups and women (2). Recent meta-analyses have attempted to answer questions regarding the association of subclinical thyroid dysfunction and cardiovascular risk (3, 4). In a recent meta-analysis which analyzed data from prospective cohort studies, the relative risk (RR) of cardiovascular disease among those with subclinical hypothyroidism was 1.20 (95% CI 0.97-1.49), but the RR was higher (1.50) for those in the lowest age group (4). The largest single study contributing data to this meta-analysis was the Cardiovascular Health Study comprising approximately 3,000 participants (5). Since publication of this meta-analysis, the association was examined in the EPIC-Norfolk cohort in England (N=11,500) (6). In this recent 2009 study, there was no significant association between subclinical hypothyroidism and cardiovascular disease; however, there were significant associations between subclinical hypothyroidism and dyslipidemia and high blood pressure. The literature is unclear on whether any association between subclinical thyroid dysfunction and cardiovascular disease or all-cause mortality is mediated through cardiac risk factors, such as dyslipidemia, hypertension, adiposity, and/or diabetes. In particular, the effect of subclinical thyroid dysfunction and LDL-cholesterol levels is currently a controversial topic. Measuring thyroid function the ARIC cohort should help shed light on these associations. Further, no large, prospective cohort analysis subclinical hypothyroidism in African Americans has previously been conducted.

A goal of this project is to comprehensively examine and characterize risk factor associations between subclinical thyroid dysfunction and clinical outcomes including possible “threshold effects,” to inform cut-points for screening and diagnosis.

Subclinical thyroid dysfunction and insulin resistance/diabetes risk*

In experimental and clinical studies, low thyroid hormone, or clinical hypothyroidism, has been found to induce a resistance to insulin action on glucose uptake in peripheral tissues (7, 8). One study evaluating the effects of subclinical hypothyroidism on insulin action found that subclinical hypothyroidism had very similar effects as clinical hypothyroidism with increased insulin resistance in fasting and post-glucose challenge states and with decreased glucose transport rates in monocytes (9). To our knowledge, no large prospective studies have examined this association. Given the shared associations of subclinical hypothyroidism and insulin resistance with cardiovascular risk factors, including dyslipidemia and elevated blood pressure, as well as cardiovascular disease, clarifying the association between hypothyroidism and insulin resistance/diabetes is of clinical interest.

**This portion of the project will be led by Johns Hopkins General Internal Medicine Fellow, Ranee Chatterjee*

Subclinical Hyperthyroidism and Arrhythmias, Stroke, and Congestive Heart Failure

Subclinical hyperthyroidism is thought to be far less common than subclinical hypothyroidism (10). Although overt (clinical) hyperthyroidism is a known risk factor for atrial fibrillation (11) and epidemiologic studies provide strong evidence that subclinical thyroid dysfunction is a risk factor for atrial fibrillation (12-14), the association between subclinical thyroid dysfunction and atrial fibrillation in cohorts that include a large sample African Americans has not been studied. The increased risk of atrial fibrillation resulting in arterial embolic events is thought to account for the increased risk of cerebrovascular events in people with thyrotoxicosis (15). To our knowledge, the risk of cerebrovascular events in people with subclinical hyperthyroidism has not been well described. One cohort, with approximately 3000 participants did not find an increased risk of heart failure (CHF) among those with subclinical hyperthyroidism compared to those who were euthyroid (16); however, no larger-scale cohorts have investigated this association.

A goal of this project is to comprehensively examine and characterize associations between subclinical hyperthyroidism and cardiovascular and cerebrovascular outcomes, such as arrhythmias, stroke, and CHF, which have been studied only to a limited extent and in smaller cohorts.

Subclinical Thyroid dysfunction and cognitive functioning and depression**

Individuals with a history of general fatigue, alterations in cognitive functioning, and/or depression are frequently evaluated for thyroid disease. Nonetheless, the relationship between subclinical thyroid dysfunction and these outcomes remains largely uncharacterized in a general population.

*** This portion of the project will be led by Johns Hopkins PhD student, Lisa Wyman*

Subclinical Thyroid dysfunction and fracture risk

Overt hypothyroidism and subclinical hypothyroidism have been associated with decreased bone density and increased risk of osteoporosis (17-19). Analysis of cross-sectional data from NHANES III found that women who had low-normal TSH levels were 5 times as likely to have osteoporosis and 3 times as likely to have osteopenia compared to women with high-normal TSH levels, after adjusting for age, BMI, and race/ethnicity (19). One case-cohort study found that hyperthyroidism was associated with increased fracture risk; however, the risk of fracture among those with subclinical hyperthyroidism was not described (20).

An aim of this project will be to quantify the fracture risk among individuals with subclinical thyroid function at baseline using hospitalization data available in the ARIC cohort. In the planned Visit 5, we will be able to evaluate the cross-sectional association between TSH measurements with the planned measurements of bone density.

Natural History of Thyroid Dysfunction in a General Population

To our knowledge, there are few studies which have conducted multiple measures of thyroid function in a general (unselected) population and no large, epidemiologic studies

which have rigorously characterized trajectories in thyroid function over the lifespan, from mid-life to old-age. The ARIC Study provides the unique opportunity to examine natural changes in thyroid function in a population setting while accounting for treatment of clinical thyroid disease (using self-reported data and medication use during visits and annual follow-up). We will measure thyroid function at 3 points in time among the subsample of individuals alive at Visit 2, CARMRI, and Visit 5. These data will allow us to assess to characterize the trajectories of thyroid function from mid-life to old-age in a general population.

Significance:
The ARIC Study is one of the most important and comprehensive studies of cardiovascular disease in the U.S. By measuring markers of thyroid function at multiple points in the life-span of ARIC participants, this proposal aims to leverage the data already available to create a novel community-based study of thyroid function and aging ("ARIC Thyroid"). We will specifically investigate whether subclinical thyroid disorders are independently associated with an increased risk of clinical outcomes. These data will directly inform the controversy regarding screening for subclinical thyroid dysfunction.

Experimental Design (include sample size justification):

Subclinical Thyroid Disease and Outcomes Study:
Prospective analyses will be conducted according to the original design of the ARIC Study with Visit 2 as baseline. To maximize power and leverage the full advantages of the ARIC Study design, all participants at Visit 2 with available stored serum will be included. Additional analyses will be conducted using CARMRI study, where the CES-D was conducted and additional measures of subclinical cardiovascular disease are available. We will analyze trajectories (slope) of thyroid function among persons who attended the Visit 2, CARMRI, and Visit 5. Repeating measurement of all thyroid function measures at Visit 5 will allow us to further characterize long-term change (from Visit 2) and allow us to rigorously examine the cross-sectional associations between thyroid function and neuro-cognitive function, depression and physical functioning in the elderly.

Methods:
Data to be collected by the ancillary study (attach questionnaires and forms):
Measurements of TSH, free T4, total T3, and anti-thyroid peroxidase antibodies in serum from Visit 2, CAMRI, and Visit 5.

Laboratory analysis of TSH, free T4, total T3, and anti-thyroid peroxidase antibodies (Anti-TPO) to be conducted by Dr. Steffes' laboratory.

Statistical analyses
Visit 2 Analyses: We will conduct prospective cohort analyses according to the original ARIC design, with Visit 2 as baseline. Main outcomes of interest will be cardiovascular disease, congestive heart failure, diabetes, and fracture-related hospitalization. The main exposure will be TSH levels, particularly among those individuals with an abnormal TSH

but normal free T4 and free T3 levels. Individuals will be classified as subclinical hypothroid, subclinical hyperthyroid, and euthyroid on the basis of these measurements. In our main analyses, individuals with clinical thyroid dysfunction will be excluded although additional analyses among persons with clinical disease are of interest. We will also assess the cross-sectional relationships between TSH and cardiovascular risk factors (hypertension, hyperlipidemia, impaired glucose metabolism, obesity). Baseline thyroid function and change cognitive function will be conducted employing models of 6-year change in levels (Visit 2 to Visit 4). We will also create a binary variable to classify individuals as having cognitive decline or not. We will conduct a secondary analysis categorizing individuals into quartiles of decline and compare those with greatest cognitive decline to those with minimal or no decline. Similar analyses of change in cardiovascular risk factors are also of interest. All analyses will be accomplished using standard statistical methods including Cox proportional hazards and logistic regression to adjust for potential confounding factors.

Individuals with overt thyroid disease as determined from self-reported medical history or medication use at baseline will be excluded from all analyses of subclinical thyroid dysfunction. Separate analyses will be conducted to examine treatment among individuals with clinical disease and clinical outcomes among this subpopulation. We will also examine risk associations (clinical consequences) of untreated clinical hypo- and hyperthyroid dysfunction, although this population of individuals may be quite small and our analyses underpowered to detect true associations.

CARMRI Analyses: The focus of analyses in CARMRI will be the cross-sectional association of subclinical thyroid function and depression, led by PhD student, Lisa Wyman (Advisor: Dr. Selvin). Unlike previous visits in ARIC, the CES-D was administered during the CARMRI visit to measure depressive symptoms. We will use logistic regression models to examine the association of subclinical hypothyroidism with depression after adjustment for relevant confounders. Individuals meeting clinical definitions of thyroid disease at CARMRI and those with a history of clinical thyroid disease via self-report will be excluded. Analyses will be conducted incorporating sampling weights to account for the CARMRI stratified sampling design (high IMT and non-high IMT). Comparisons of results with the Vital Exhaustion Questionnaire (administered Visit 2) will also be conducted.

Visit 5 Analyses: The focus of Visit 5 analyses will be the cross-sectional associations of thyroid function with measures of neuro-cognitive functioning in collaboration with ARIC NCS investigators.

Trajectory of thyroid function from mid-life to old-age: we will utilize the repeated thyroid function measurements among those persons who attended all three visits: Visit 2, CARMRI, and Visit 5 to characterize the natural history of thyroid functioning from mid-life to older-age in the ARIC cohort. To our knowledge, no previous study has characterized the trajectory of these measurements in an unselected population and examined changes over time. Further, we anticipate that rigorous characterization of change in thyroid function will set the stage for additional analyses of change in thyroid function and clinical outcomes.

Literature Cited

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Please send (electronically and by surface mail) the completed proposal to:

Aaron R. Folsom, M.D. (Principal Investigator) folsom@epi.umn.edu
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For Coordinating Center Use Only

Approved? _____ Date _____ If approved, ancillary study #

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