

**ARIC Manuscript Proposal # 3175**

**PC Reviewed:** 6/12/18                      **Status:** \_\_\_\_\_                      **Priority:** 2  
**SC Reviewed:** \_\_\_\_\_                      **Status:** \_\_\_\_\_                      **Priority:** \_\_\_\_\_

**1.a. Full Title:** Association of Abnormal Thyroid Function with Dementia and MCI in the Atherosclerosis Risk in Communities (ARIC): Neurocognitive Study (NCS)

**b. Abbreviated Title (Length 26 characters):** Thyroid Function and Dementia

**2. Writing Group:** Kristen M. George, Aaron R. Folsom, Pamela L Lutsey, Elizabeth Selvin, Priya Palta, B. Gwen Windham

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

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**3. Timeline:** Begin analysis following ARIC committee approval

**4. Rationale:**

The thyroid gland is an endocrine organ that regulates metabolism. [1] Triiodothyronine (T3) and thyroxine (T4) help regulate cellular energy use affecting almost every organ in the body. [2][3] T3 and T4 are produced from dietary iodine absorbed through the small intestine and circulated to the thyroid where the iodine is concentrated, oxidized, and incorporated into thyroglobulin (Tg). [4] Thyroid hormone is found in three states: stored as droplets within thyroid follicles, bound to carrier proteins circulating in the blood, or circulating freely (biologically active) as free T3 (FT3) and free T4 (FT4). [1] T4 comprises 90% of thyroid hormone, though T3 is more biologically active. [5]

A negative feedback loop regulates thyroid hormone activity. Thyrotropin-releasing hormone (TRH) produced in the hypothalamus stimulates the anterior pituitary gland to release thyroid-stimulating hormone (TSH). [5] TSH, in turn, stimulates release of FT3 and FT4 from

the thyroid increasing levels of biologically active thyroid hormone. [5] This change in hormone levels increases metabolism of almost all body tissues which can result in increased body temperature, strengthened heartbeat, accelerated pulse, increased digestion of macronutrients, and activation of the nervous system. [1][5] The loop closes when biologically active T3 and T4 act back on the hypothalamus inhibiting further TRH release and shutting off the system. [5][6]

Thyroid dysfunction is common, especially among older adults, and can have serious clinical implications. [7] Thyroid function is generally classified as euthyroidism (normal thyroid function), hypothyroidism (underactive thyroid), and hyperthyroidism or thyrotoxicosis (overactive thyroid). Elevated TSH and subnormal FT4 levels characterize overt hypothyroidism, while elevated TSH with normal FT4 characterize subclinical hypothyroidism. [8] Subnormal TSH and elevated FT4 levels characterize overt hyperthyroidism, while subnormal TSH with normal FT4 characterize subclinical hyperthyroidism. [9] See Table 1 for prevalence of thyroid disorders in the U.S.

<b>Thyroid Disorder</b>	<b>Estimated Prevalence</b>
Overt Hypothyroidism	0.3%
Subclinical Hypothyroidism	4.3%
<b>Total Hypothyroidism</b>	<b>4.6%</b>
Overt Hyperthyroidism	0.5%
Subclinical Hyperthyroidism	0.7%
<b>Total Hyperthyroidism</b>	<b>1.2%</b>
<b>Total Disorder</b>	<b>5.8%</b>

**Table 1.** Prevalence of thyroid dysfunction in those ages  $\geq 12$ : NHANES III (1988-1994). [10]

Thyroid dysfunction is more prevalent in women compared to men and among non-Hispanic whites compared to African Americans. [10] Further, average TSH levels and prevalence of anti-thyroid antibodies, indicators of thyroid disorder, are higher in women compared to men, a

disparity that increases with age, and higher among whites than African Americans. [10] While thyroid dysfunction is common, most cases are subclinical.

In iodine-replete countries like the U.S., autoimmune thyroid disease (AITD) is the most common cause of thyroid dysfunction with an estimated prevalence of 5%. [11] AITD is caused by an immune attack on the thyroid and results in infiltration of the thyroid tissue by lymphocytes. [11] A combination of genetic susceptibility and environmental factors, including radiation, smoking, infection, stress, and drugs, can trigger the autoimmune response. [11][12] The two main clinical presentations of AITD are Grave's disease (GD), which presents clinically as hyperthyroidism, and Hashimoto's thyroiditis (HT), which presents clinically as hypothyroidism. [11] All forms of AITD are associated with the presence of serum anti-thyroid peroxidase (TPO) and thyroglobulin (Tg) antibodies, though the presence of antibodies does not necessitate disease. [13][14] Anti-TPO antibodies are more common and a stronger indicator of thyroid disease than anti-Tg antibodies. [14] Anti-TPO is prevalent in 90-95% of AITD patients and an estimated 17% of women and 9% of men without known AITD. [13][14]

Thyroid dysfunction can cause a range of mood and cognitive disturbances, especially in severe cases. Hypothyroidism is associated with increased rates of anxiety and depression as well as mild to moderate deficits in memory and executive function. [15] Hyperthyroidism can also cause anxiety and depression as well as irritability, agitation, and deficits in concentration and executive function. [15] Increased screening and better treatment has reduced the rate of thyroid-related cognitive symptoms by reducing the incidence of severe disorder and reversing cognitive symptoms with effective treatment. [15] Despite these advancements, there is still interest in the relationship between thyroid disorder and dementia due to the thyroid's well-established

influence on brain development and function including neuronal maturation and myelination.

[16] [17]

There are two mechanisms by which thyroid disorders may be associated with dementia: action of thyroid hormones on the brain causing impairment [18] or autoimmunity causing AITD and encephalopathy leading to permanent damage. [19]

**Table 2.** Literature review of the association between thyroid function and cognition

<b>Citation</b>	<b>Study Design</b>	<b>Population</b>	<b>Exposure(s)</b>	<b>Outcome(s)</b>	<b>Results</b>
[16] Beydoun, 2015	Prospective Cohort (n = 2,630)	Whites and Blacks in Baltimore, MD (age: 30-64)	TSH, T4, FT4, T3	Cognitive Test Scores	Higher TSH associated with faster cognitive decline
[20] Jan de Jong, 2009	Prospective Cohort (n = 665)	Japanese-American men (age: 71-93)	FT4, T4	Incident Dementia and brain autopsy in sub-sample (n = 143)	Greater T4 and FT4 (per SD) associated with 20% and 30% higher hazard of dementia; greater T4 associated with higher number of plaques and tangles
[21] Chaker, 2016	Prospective Cohort (n = 9,446)	Rotterdam Study (mean age: 65)	TSH, FT4, anti-TPO antibodies	Incident Dementia and MRI	Higher TSH, FT4 associated with increased hazard of dementia, while anti-TPO positivity had decreased hazard. Thyroid function not associated with vascular brain abnormalities.
[22] Naphthali, 2014	Cross-sectional (n = 3,253)	Australians in Hunter Community Study (age: 55-84)	anti-TPO antibodies	Cognitive Test Scores	No association between anti-TPO positivity and cognitive test score

[23] Pasqualetti, 2015	Meta-Analysis (n = 13 studies)	N/A	Subclinical Hypothyroidism	Incident Dementia and Cognitive Test Scores	Subclinical Hypothyroidism was not associated with cognitive decline and dementia
[24] Yeap, 2012	Prospective Cohort (n = 3,401)	Australian Men (age: 70-89)	FT4, TSH	Dementia-related ICD codes	Higher levels of FT4 was associated with dementia diagnosis, but TSH was not associated.
[25] Volpato S, 2002	Prospective Cohort (n = 628)	Women's Health and Aging Study (age: ≤65)	T4, TSH	Cognitive Test Scores	Higher levels of T4 were associated with greater cognitive decline, but no association with TSH.
[26] Moon, 2014	Prospective Cohort (n = 313)	Korean Longitudinal Study on Health and Aging (KLoSHA) (age: ≤65)	T4, TSH	Dementia and MCI	Low TSH levels were associated with incident dementia and MCI, but T4 was not associated
[27] Tan, 2008	Prospective Cohort (n = 1,864)	The Framingham Study (mean age: 71)	TSH	Dementia	Lowest and Highest TSH levels associated with dementia in women (not men).

SD: standard deviation      AD: Alzheimer's disease      MCI: Mild Cognitive Impairment

The majority of studies examining the relationship between thyroid function and dementia have focused on thyroid hormones as a risk factor for dementia, not markers of AITD. Further, while many studies have found a relationship between elevated TSH levels and dementia or cognitive decline, the literature regarding other thyroid hormones (necessary for diagnosing dysfunction) is

mixed (see Table 2). Many studies are relatively small ( $n < 3,000$ ), age at baseline was primarily  $\geq 65$  years, which is when risk of dementia increases significantly and cognitive changes may already be underway [28], and follow-up time was generally short ( $< 5$  years). Using data from the Atherosclerosis Risk in Communities (ARIC): Neurocognitive Study (NCS), we have the unique opportunity to examine the association between AITD and dementia as well as thyroid hormones and dementia using over 25 years of follow-up and adjudicated dementia outcomes.

## **5. Main Hypothesis/Study Questions:**

**Aim 1:** Determine whether markers of autoimmunity causing autoimmune thyroid disease (AITD) is associated with dementia.

**Hypothesis 1:** We hypothesize that participants that are anti-thyroid peroxidase (TPO) antibody positive, an indicator of an autoimmune response, will have an increased risk of dementia.

**Hypothesis 2:** We hypothesize that participants that are anti-thyroid peroxidase (TPO) antibody positive will have increased risk of dementia with primary or secondary cerebrovascular disease etiology compared to other primary/secondary etiologies.

**Aim 2:** Assess the association between thyroid dysfunction and dementia.

**Hypothesis 1:** We hypothesize that participants with subclinical and overt hypothyroidism and hyperthyroidism (defined using Roche cut-points) will be at increased risk of dementia compared to participants with normal thyroid function.

**Hypothesis 2:** We hypothesize that participants in the highest and lowest quartiles of TSH, FT4, and T3 will have increased risk of dementia than participants with TSH, FT4, and T3 levels in the middle ranges, regardless of treatment for clinical disease.

**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 Study: baseline visit 2 (1990-1992) through visit 6 (2016-2017)

**Exclusions:** Participants will be excluded if they are missing serum TSH, FT4, T3, or TPO measures, had prevalent dementia (identified via ICD codes) at visit 2, prevalent stroke, coronary heart disease (CHD), myocardial infarction (MI), or atrial fibrillation at visit 2, or were non-white or African Americans participants as well as African Americans in MD or MN).

**Exposure:** Serum samples stored at  $-70^{\circ}\text{C}$  since collection at visit 2 were thawed and tested at Advanced Research Diagnostics Laboratory (University of Minnesota) between 2011 and 2013. Assays from Roche Diagnostics were used on an Elecsys 2010 Analyzer using sandwich

immunoassay method for TSH and competition immunoassay methods for FT4, total T3, and anti-TPO antibodies. [29] Interassay coefficients of variation were  $\leq 10\%$ . [29] Anti-TPO antibody positivity will be defined as  $>34$  kIU/L to be considered antibody positive based on assay manufacturer guidelines. [30] Five clinical categories, subclinical hypothyroidism, subclinical hyperthyroidism, overt hypothyroidism, overt hyperthyroidism, and euthyroidism, will define thyroid dysfunction based on TSH and FT4 levels (See Table 2 for cut points). [10] We will also examine distribution-based quartiles of TSH, FT4, and T3 levels. While T3 will not be used in the definition of clinical thyroid dysfunction, the hormone as an indicator of hyperthyroidism and a useful marker of dysfunction. [31]

<b>Clinical Categories</b>	<b>Number of ARIC participants, N (%)</b>	<b>TSH Cut Point (mIU/L)</b>	<b>FT4 Cut Point (ng/dL)</b>
<b>Overt Hypothyroidism</b>	282 (2.2)	$> 5.1$	$< 0.85$
<b>Subclinical Hypothyroidism</b>	583 (5.6)	$> 5.1$	0.85 - 1.4
<b>Euthyroidism</b>	11,033 (88.8)	0.56 - 5.1	0.85 - 1.4
<b>Subclinical Hyperthyroidism</b>	433 (3.4)	$< 0.56$	0.85 - 1.4
<b>Overt Hyperthyroidism</b>	237 (1.9)	$< 0.56$	$> 1.4$

**Table 2.** Definitions for clinical categories of thyroid dysfunction [10] [29] and number of ARIC participants falling within each category

**Outcome:** We will use dementia and mild cognitive impairment (MCI) outcomes identified using three levels of criteria. The first level, involved adjudicated outcomes from visits 5 (2011-2013) and 6 (2016-2017) NCS evaluations including the longitudinal cognitive assessments from visits 2, 4, 5, and 6. [32] A standardized definition for dementia and MCI was used for level 1 classification to generate computer algorithmic diagnoses; a panel of physicians and

neuropsychologists reviewed each case of suspected cognitive impairment as well as a random sample of cognitively normal participants. [32]

Level 2 dementia and MCI includes cases identified in level 1 as well as participants who did not attend ARIC-NCS and were identified through telephone interview for cognitive status (TICS), informant telephone interview using a modified version of the Clinical Dementia Rating (CDR), and a random sample used to correct for missed cases. [32] This identification primarily occurred during visits 5 and 6 (2011–2016). [32] Finally, level 3 includes levels 1 and 2 as well as participants identified through surveillance for hospitalization discharge codes (ICD-9) or death certificate codes related to dementia which were primarily identified prior to visit 5. [32]

Separate analyses will be run using two definitions of dementia and MCI outcomes. The first definition will include all incident dementia cases from visit 2 through 6 (level 3 criteria). The second definition will only include adjudicated dementia and MCI cases (level 1 criteria), which were identified at ARIC visits 5 and 6 and include information on etiology (i.e. Alzheimer's disease vs. cerebrovascular vs. other determined by additional review of a participant's brain magnetic resonance imaging (MRI) scan).

**Covariates from visit 1:** age, sex, race (MS-blacks, NC-whites, NC-blacks, MN-whites, and MD-whites), APOE  $\epsilon$ 4, income, and education

**Covariates from visit 2:** body mass index (BMI), smoking status, hypertension (defined as systolic blood pressure  $\geq$  140 mm Hg, or diastolic blood pressure  $\geq$  90 mm Hg, or self-report of antihypertensive medication use), diabetes, prevalent coronary heart disease (CHD), incident stroke, drinking status, HDL cholesterol, and total cholesterol

## **Analysis:**

Analyses will follow ARIC NCS analysis working group recommendations.

*Aim 1: Determine whether autoimmunity causing autoimmune thyroid disease (AITD) is associated with dementia, will be assessed using all dementia cases (level 3) as well as adjudicated dementia cases only (level 1).* For aim 1, hypothesis 1, Cox regression with a competing risk of non-dementia related death will be used to assess the hazard of level 3 dementia in relation to anti-TPO antibody status (positive/negative) between visits 2 and 6. Analysis will then be repeated using level 1 cases (from visits 5 and 6) in a relative risk regression to assess anti-TPO antibody status and adjudicated dementia. Relative risk regression will be conducted using generalized linear models with a Poisson distribution and a log link. Inverse probability weights will be included to account for possible attrition from visit 2. For Aim 1, hypothesis 2, relative risk regression will be used to assess the association between anti-TPO positivity and each subtype of adjudicated dementia and MCI (cerebrovascular etiology and non-cerebrovascular etiology) in two separate models.

*Aim 2: Assess the association between thyroid dysfunction and dementia, we will again use level 3 and level 1 dementia cases in separate analyses.* For aim 2 hypothesis 1, participants will be divided into five clinically significant categories of thyroid function, subclinical hypothyroidism, subclinical hyperthyroidism, overt hypothyroidism, overt hyperthyroidism, and euthyroidism. Using level 3 dementia cases, Cox regression with a competing risk of non-dementia related death will be used to assess the hazard of dementia by thyroid function category between visits 2 and 6 with euthyroidism as the reference. This analysis will be repeated using relative risk regression with inverse probability weights to assess level 1 adjudicated dementia cases and categorical thyroid function. To address aim 2 hypothesis 2, we will create categorical

variables for TSH, FT4, and T3 divided into distribution-based quartiles. Cox regression with a competing risk of non-dementia related death will be used to assess the hazard of level 3 dementia by categorical TSH, FT4, and T3 between visits 2 and 6 in three separate models. Analysis will be repeated for categorical TSH, FT4, and T3 with adjudicated dementia and MCI cases using relative risk regression. A sensitivity analysis will be conducted for aim 2, by repeating analyses for hypotheses 1 and 2 with excluding participants who self-report taking thyroid medication at baseline. We will also do a sensitivity analysis using various distribution-based categorical variables for thyroid hormones, particularly at extreme ends of the distributions, as well as examine non-linear associations.

For all analyses, models will be adjusted for baseline covariates (from visits 1 and 2):

Model 1: age, sex, race, APOE ε4, income, and education

Model 2: plus BMI, smoking status, hypertension, diabetes, prevalent CHD, drinking status, HDL cholesterol, and total cholesterol.

We will also investigate BMI as a mediator and effect modification of the associations by gender with an anti-TPO positivity interaction term for aim 1 and a gender by categorical thyroid hormone level interaction term for aim 2.

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

There are several papers that examine the relationship between thyroid function and cardiovascular-related diseases, but none looking at cognitive outcomes.

**MS #2951:** Thyroid Hormones and Prostate Cancer

**MS #2913:** Prevalence and Risk Factors of Thyroid Dysfunction in Older Adults in the Community

**MS #2781:** Thyroid Function and Atrial Fibrillation: a Mendelian Randomization Study

**MS #2492:** Thyroid Dysfunction, Cardiovascular Risk Factors, and Incident Events

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

**MS #2176 r:** Identification and Characterization of Genetic Risk Associated with Measures of Thyroid Function and Disease

**MS #2151:** Thyroid Dysfunction and Venous Thromboembolism

**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\* AS# 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.csc.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.csc.c.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to PubMed central.

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