ARIC Manuscript Proposal #2492

PC Reviewed: 2/10/15   **Status: <u>A</u>**   **Priority: <u>2</u>**
SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.a. Full Title: Thyroid Dysfunction, Cardiovascular Risk Factors, and Incident Events: The Atherosclerosis Risk in Communities (ARIC) Study

  b. Abbreviated Title (Length 26 characters): Thyroid & CVD

2.   Writing Group: 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; others welcome

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

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3.   Timeline: Data are available. The analysis will start immediately following project approval and will take 3-6 months. An abstract will be prepared for submission to a national scientific meeting within 3 months of analysis completion. The manuscript will be prepared by the time that the project is presented at a national scientific meeting.

4.   Rationale (comprehensive for study planning, will be honed down to ~1 page double-spaced for eventual manuscript):

        The thyroid gland is intricately related to the cardiovascular system, sharing a common embryological origin, and regulating major functions of the heart and vasculature.[1] In response to thyroid stimulating hormone (TSH) release from the

pituitary, the thyroid couples iodinated tyrosine molecules into hormones that enter the circulation and exert broad physiologic influence. Given the potential role of thyroid dysfunction in diseases such as sinus bradycardia, atrial fibrillation, and heart failure, thyroid tests are commonly obtained in cardiovascular care.

Thyroid function also appears to have important effects on each aspect of the metabolic syndrome, including abdominal obesity, hyperglycemia, low HDL-C, high TG, and hypertension.[2,3] Regarding the latter, hypothyroidism is tied to diastolic hypertension whereas hyperthyroidism is tied to systolic hypertension. Low normal free T4 (FT4) levels are associated with a more atherogenic lipid profile and insulin resistance.[4] The 2013 ACC/AHA Cholesterol Treatment Guideline notes hypothyroidism as one of the most commonly encountered secondary causes of elevated low-density lipoprotein cholesterol (LDL-C) and/or triglycerides.[5] Lipid changes in thyroid dysfunction appear to occur quickly as a 3-week hypothyroid state after thyroidectomy promotes a more atherogenic lipid profile.[6]

Downstream of risk factors, existing evidence shows an association of thyroid dysfunction with both subclinical coronary atherosclerosis and incident coronary disease. In apparently healthy young and middle-aged euthyroid individuals, low-normal FT4 and TSH correlate with a higher prevalence of subclinical coronary disease and the extent of coronary calcification.[7] Multiple studies show a link between subclinical hypothyroidism and higher risk of incident coronary disease,[8-12] which does not appear to vary by thyroid peroxidase antibody (TPOAb) status.[13] Meta-analyses indicate that risk associations are more modest in higher-quality studies[10] and that the association may be confined to younger individuals.[11] Consistent with effect modification by age, in older populations, subclinical hypothyroidism does not appear to be associated with higher risks of incident coronary heart disease, heart failure, cardiovascular mortality,[14] weight,[15] or all-cause and cardiovascular mortality.[16]

In persons with subclinical but not overt hypothyroidism, thyroid replacement therapy reduces LDL-C levels[17] and improves other cardiovascular risk factors such as waist-to-hip ratio.[18] Currently, thyroid hormone analogs are being evaluated for treatment of dyslipidemia, atherosclerosis, and obesity.[3,19] Over 3 months, a thyroid hormone analogue, eprotirome, has been shown to reduce atherogenic lipoproteins in statin-treated patients.[20]

In addition to cardiometabolic risk, atherosclerosis, and coronary disease, decreased thyroid function appears to be associated with left ventricular diastolic dysfunction at rest and effort-induced systolic dysfunction. Hyperthyroidism, on the other hand, may be an independent risk factor for left ventricular hypertrophy (LVH)[21] with impairments in ventricular relaxation and exercise performance seen in subclinical hyperthyroidism.[22] Indeed, perhaps in part related to greater hemodynamically-related atrial stress, as well as direct cellular effects, multiple studies implicate subclinical hyperthyroidism in atrial fibrillation, a potent risk factor for stroke.[22-24] In the context of thyroid related alterations in left ventricular structure and function, and atrial rhythm, both higher and lower TSH levels are associated with higher risks of heart failure. [25-27] In

fact, heart failure is thought to be the most common cause of cardiovascular mortality in overt and subclinical hyperthyroidism.[28]

Reflecting the net impact of thyroid function on the cardiovascular system, and other organs, multiple studies have established that the functional status of the thyroid is associated with mortality. In euthyroid individuals, FT4 and T3 in the normal range are inversely related to all-cause mortality.[29] In contrast, subclinical hyperthyroidism is associated with an elevated risk for all-cause and cardiovascular mortality,[22,30] while a low normal TSH also appears to be associated with higher risk for all-cause mortality.[31] Subclinical hypothyroidism in particular can be considered a marker of individuals with greater risk for cardiovascular and all-cause mortality, with multiple meta-analyses supporting this relationship.[10-12,32]

The above relationships are summarized in the following Directed Acyclic Graph:
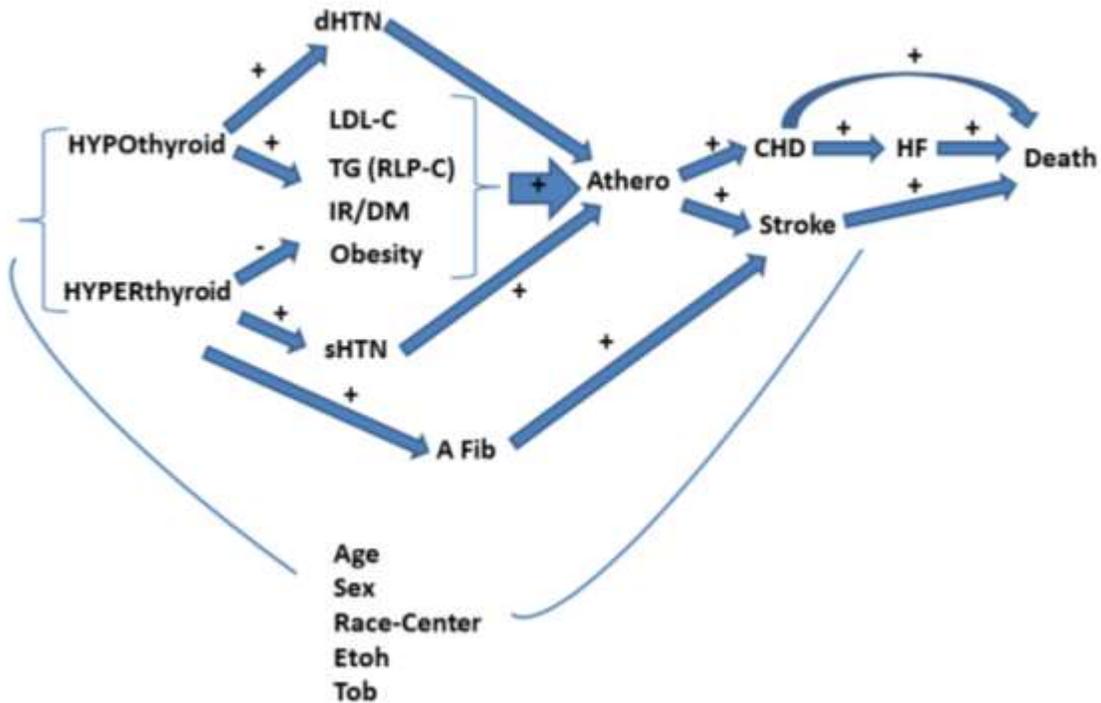
dHTN = diastolic hypertension; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; RLP-C = remnant lipoprotein cholesterol; IR/DM = insulin resistance / diabetes mellitus; sHTN = systolic hypertension; A Fib = atrial fibrillation; Athero = atherosclerosis; CHD = coronary heart disease; HF = heart failure (there may also be direct effects of factors such as hypertension on non-ischemic forms of heart failure, which are not illustrated); Etoh = alcohol use; Tob = tobacco smoking.

However, important unresolved questions remain at the intersection of the thyroid gland and the cardiovascular system. Although knowledge in this field has greatly expanded over the past decade, there has been less focus on carefully delineating the relationships between thyroid function status and cardiovascular risk factors, including traditional risk factors and novel risk factors. To what extent effects of the thyroid on clinical CVD events may be mediated by these factors versus the result of direct effects is uncertain. In addition, there is relatively less data on thyroid dysfunction and stroke risk. Studies linking hyperthyroidism with greater carotid intima media thickness[33] and atrial

fibrillation would lead one to anticipate the possibility of higher stroke risk; however, high-quality prospective cohort data are needed on this issue.

Furthermore, it may also be an important limitation that in assessing thyroid function status, triiodothyronine (T3) has generally been a measurement left out of epidemiologic studies to date. T3 is the final and active form of thyroid hormone that is thought to be the predominant mediator of many of its peripheral effects. It still remains uncertain whether thyroid replacement therapy with T4 alone, or a combination of T3 and T4, is optimal.[34]

In addition, there is a gap in evidence-based guidance on the role of thyroid evaluation in assessment of cardiovascular risk in asymptomatic patients. Despite the literature linking thyroid dysfunction to cardiovascular risk factors and future risk of coronary heart disease, the 2013 ACC/AHA Risk Assessment Guideline does not discuss evaluation of thyroid markers in its 184 page report. Additional analyses from high-quality prospective cohort studies could provide foundational knowledge to allow future guideline committees to guide clinicians on when and how thyroid markers should be used in cardiovascular disease risk assessment and preventive care.

Thus, we aim to leverage data from the ARIC thyroid ancillary study to expand knowledge on the cross-sectional and longitudinal associations of thyroid markers with cardiovascular risk factors and outcomes. Importantly, the ARIC thyroid ancillary study has assessed a comprehensive panel of thyroid markers, including T3, FT4, TSH, and TPOAb. The rigorous prospective, cohort design of the ARIC study, combined with the availability of a comprehensive thyroid panel, positions the study build importantly on advances in knowledge over from the last decade, and move the field forward.

5.   Main Hypothesis/Study Questions: To investigate the cross-sectional and longitudinal association of thyroid function with cardiovascular risk factors and events.

Specific Aim #1: Investigate cross-sectional association of thyroid function with cardiovascular risk factors. We hypothesize that there will be a positive association of hypothyroidism (stronger for overt vs subclinical) with diastolic hypertension, LDL-C (and non-HDL-C), triglycerides (marker of remnant lipoprotein cholesterol), insulin resistance, and obesity. We further hypothesize that the relationships with diastolic hypertension, LDL-C, triglycerides, and insulin resistance will be independent of obesity. In contrast, we hypothesize that there will be an inverse association of hyperthyroidism with these cardiometabolic risk factors, with the caveat of hypertension, where we hypothesize that there will be a positive association with systolic hypertension. Furthermore, we predict a positive association of hyperthyroidism with prevalent atrial fibrillation.

Specific Aim #2: Investigate the longitudinal association of thyroid function with cardiovascular events. We hypothesize that overt hypothyroidism and overt hyperthyroidism will be treated and therefore will have modest to null associations with cardiovascular events. In contrast, we hypothesize that subclinical hypothyroidism will

have a positive association with cardiovascular events that will be attenuated or abolished after adjustment for hypertension, dyslipidemia, insulin resistance, and obesity. In contrast, we hypothesize that subclinical hyperthyroidism will have a protective association with major CHD events (myocardial infarction, fatal coronary heart disease) but a more neutral association with stroke given the net result of a higher stroke risk due to atrial fibrillation. We further hypothesize that both subclinical hypothyroidism and subclinical hyperthyroidism will be associated with higher mortality, most commonly through heart failure.

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 and longitudinal analysis of thyroid measures, cardiovascular risk factors, and cardiovascular events. Thyroid measures were obtained at Visit 2 (1990-92), which will be considered the baseline for this study.

Study Population (Inclusion/Exclusion Criteria): We will include all participants who attended Visit 2 with thyroid measurements performed on stored serum. We will exclude those with a history of MI/CHD, stroke, or heart failure present at or before Visit 2.

Outcomes:

- **Cross-sectional: We will focus on CVD (or "cardiometabolic") risk factors, namely diabetes, lipids, blood pressure, BMI, waist circumference.**

  The lipids that we will examine are TC, LDL-C, non-HDL-C, TG, estimated VLDL-C, HDL-C, TC/HDL-C, TG/HDL-C.

- **Longitudinal: We will focus on major atherosclerotic CVD events, including major CHD (myocardial infarction, fatal coronary heart disease) and stroke.**

  As secondary outcomes, we will consider heart failure and all-cause mortality.

Exposure: Thyroid function status as determined by thyroid markers which were measured in 2012-13 from stored serum specimens. Assays from Roche Diagnostics were used on an Elecsys 2010 Analyzer (Visit 2) using a sandwich immunoassay method for TSH and competition immunoassay methods for FT4, T3 and TPOAb. All inter-assay coefficients of variation (CVs) were ≤10%.

We will perform continuous analyses using log-transformed T3, and we will also use the following definitions to perform categorical analyses:

- Overt Hypothyroidism: TSH>5.1 mIU/L & FT4<0.85 ng/dL
- Subclinical Hypothyroidism: TSH>5.1 mIU/L & 0.85 ng/dL≤FT4≤1.4 ng/dL

- Euthyroidism: 0.56 mIU/L≤TSH≤5.1 mIU/L, 0.85 ng/dL≤FT4≤1.4 ng/dL
- Overt Hyperthyroidism: TSH<0.56 mIU/L & FT4>1.4 ng/dL
- Subclinical Hyperthyroidism: TSH<0.56 mIU/L & 0.85 ng/dL≤FT4≤1.4 ng/dL
- Thyroiditis: TPOAb>34

Of note, these definitions are based on ARIC-derived cut-points, which have previously been found to be more strongly associated with the thyroid genes/genetic risk score and other risk factors suggesting better performance in general in ARIC. Cut-points from Roche (the manufacturer) will be considered secondary.

Baseline covariates (for Table 1, not all to be included in multivariable models): age (years, continuous), sex (male/female), race/field center (Maryland whites; Minnesota whites, North Carolina whites; North Carolina blacks; Mississippi blacks), smoking status (current/former/never), alcohol consumption (current/former/never), diabetes mellitus (yes/no), hemoglobin A1c (continuous), hypertension (yes/no), total cholesterol (continuous), HDL cholesterol (continuous), triglycerides (continuous), *LDL cholesterol (continuous), *VLDL cholesterol, non-HDL cholesterol (continuous), TC/HDL-C ratio (continuous), TG/HDL-C ratio (continuous), systolic and diastolic blood pressure (continuous), thyroid medication use (yes/no), anticoagulant (yes/no), anti-hypertensive (yes/no), lipid-lowering medication (yes/no), diabetes medication (yes/no), high-sensitivity C-reactive protein (continuous), body mass index (continuous), waist-hip ratio (continuous), estimated GFR-Cr by CKD-EPI equation (continuous), physical activity (categorical), left ventricular hypertrophy by Cornell criteria (yes/no), NT-proBNP (continuous), heart rate (continuous). All measured at Visit 2.

Time-varying covariates: we do not have repeat thyroid tests at Visit 3 or Visit 4. Thyroid medication use was present in 5.1% of participants at Visit 2, 6.5% at Visit 3, and 7.9% at Visit 4. However, it is generally felt that thyroid medication use was not well captured at follow-up in ARIC. We will only run models with time-varying thyroid medication use data and time-varying cardiovascular risk factors if we feel that the yield can be justified after initial modeling.

*Estimated two ways:
- Friedewald et al Clin Chem 1972;18:499-502
- Martin et al JAMA 2013;310:2061-8

Potential effect modifiers: In event analyses, based on prior literature, we will test for interaction by age. We will also examine potential interactions by race/center and sex. For analyses of serum lipids, prior literature suggests that smoking and obesity/insulin resistance are effect modifiers,[35,36] which we will take into account. If statistically significant effect modification is observed, then a stratified analysis will be performed and presented.

Summary of data analysis: By thyroid status, we will examine age, sex, and race/center adjusted covariates as frequencies (percentage) for categorical variables, mean (SD) for continuous variables following a normal distribution, and median (IQR) for continuous

variables that do not follow a normal distribution (e.g., triglycerides). We will compare baseline characteristics of study participants using χ^2 and t tests for categorical and continuous variables, as appropriate. Associations with prevalent cardiovascular disease and cardiovascular disease risk factors will be estimated from multiple regression adjusting for age, sex, and race/center. Hazard ratios for individual incident cardiovascular disease endpoints or death, loss-to-follow up or censoring will be estimated using Cox proportional hazards regression in the following sequential models:

- Model 1 (Crude unadjusted)
- Model 2 (Adjustment for mediators): diabetes, HbA1c, sBP, dBP, non-HDL-C, heart rate
- Model 3 (Adjustment for confounders): Model 2 + age, sex, race-center, HDL-C, BMI, alcohol, tobacco use, lipid-lowering medication, anti-hypertensive

For model with stroke as the endpoint, we will also include atrial fibrillation as a mediator.

As indicated above, the models will model the exposure of thyroid function group or continuous log-transformed T3 levels.

Sensitivity analyses:

1. Exclusion of those on thyroid medication at Visit 2. The reason for this is that there may be a difference in the outcomes related to endogenous versus exogenous thyroid dysfunction.

2. Limit follow-up to Visit 4. The reason for this is that nearer-term follow-up may more closely relate to baseline thyroid tests because there is less time for instance for a subclinical hypothyroid patient to progress to overt hypothyroidism and receive thyroid replacement therapy, altering the natural history. In addition, there is better medication data at and before Visit 4 than subsequent to Visit 4, which will further strengthen the analysis.

3. Categorical analysis using Roche cut-points to define thyroid function groups.

Limitations: A key limitation of the cross-sectional analyses is the lack of ability to infer temporality or definitively establish causality. It is also possible, although this cannot be proven or disproven directly in our study, that analysis of thyroid markers on stored specimens yields different values than may have been obtained at the time of specimen collection. While the longitudinal analyses allow us to infer temporarily, it will still be challenging to infer causality in this observational study, particularly given the complexity of thyroid hormone effects.

Epidemiologic studies of thyroid disease are universally challenged in linking overt hypothyroidism or overt hyperthyroidism to long-term clinical outcomes because it is expected that the majority of such individual will receive treatment to correct their thyroid disorder. Therefore, in mapping thyroid markers to long-term outcomes, prior

literature has focused on subclinical thyroid dysfunction, where therapeutic intervention is less likely. Because the time span from Visit 2 to Visit 4 is ~6 years, it is unlikely that a substantial proportion of the study population will have transitioned to a more severe thyroid status and hence received intervention.

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)?

      This is the first use of the thyroid ancillary study data in cardiovascular disease.

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* _____)
      ___   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.

We understand and will complete the manuscript in a timely fashion.

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.

This responsibility will be fulfilled.

References

1. Grais IM, Sowers JR. Thyroid and the heart. *The American journal of medicine.* Aug 2014;127(8):691-698.
2. Iwen KA, Schroder E, Brabant G. Thyroid hormones and the metabolic syndrome. *European thyroid journal.* Jun 2013;2(2):83-92.
3. Baxter JD, Webb P. Thyroid hormone mimetics: potential applications in atherosclerosis, obesity and type 2 diabetes. *Nature reviews. Drug discovery.* Apr 2009;8(4):308-320.
4. Roos A, Bakker SJ, Links TP, Gans RO, Wolffenbuttel BH. Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. *The Journal of clinical endocrinology and metabolism.* Feb 2007;92(2):491-496.
5. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology.* Jul 1 2014;63(25 Pt B):2889-2934.
6. Erbil Y, Ozbey N, Giris M, Salmaslioglu A, Ozarmagan S, Tezelman S. Effects of thyroxine replacement on lipid profile and endothelial function after thyroidectomy. *The British journal of surgery.* Dec 2007;94(12):1485-1490.
7. Zhang Y, Kim BK, Chang Y, et al. Thyroid hormones and coronary artery calcification in euthyroid men and women. *Arteriosclerosis, thrombosis, and vascular biology.* Sep 2014;34(9):2128-2134.
8. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. *Annals of internal medicine.* Feb 15 2000;132(4):270-278.
9. Walsh JP, Bremner AP, Bulsara MK, et al. Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. *Archives of internal medicine.* Nov 28 2005;165(21):2467-2472.
10. Ochs N, Auer R, Bauer DC, et al. Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. *Annals of internal medicine.* Jun 3 2008;148(11):832-845.
11. Razvi S, Shakoor A, Vanderpump M, Weaver JU, Pearce SH. The influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease: a metaanalysis. *The Journal of clinical endocrinology and metabolism.* Aug 2008;93(8):2998-3007.
12. Rodondi N, den Elzen WP, Bauer DC, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *Jama.* Sep 22 2010;304(12):1365-1374.
13. Collet TH, Bauer DC, Cappola AR, et al. Thyroid antibody status, subclinical hypothyroidism, and the risk of coronary heart disease: an individual participant data analysis. *The Journal of clinical endocrinology and metabolism.* Sep 2014;99(9):3353-3362.
14. Hyland KA, Arnold AM, Lee JS, Cappola AR. Persistent subclinical hypothyroidism and cardiovascular risk in the elderly: the cardiovascular health

study. *The Journal of clinical endocrinology and metabolism.* Feb 2013;98(2):533-540.

15. Garin MC, Arnold AM, Lee JS, Tracy RP, Cappola AR. Subclinical hypothyroidism, weight change, and body composition in the elderly: the Cardiovascular Health Study. *The Journal of clinical endocrinology and metabolism.* Apr 2014;99(4):1220-1226.

16. Waring AC, Harrison S, Samuels MH, et al. Thyroid function and mortality in older men: a prospective study. *The Journal of clinical endocrinology and metabolism.* Mar 2012;97(3):862-870.

17. Meier C, Staub JJ, Roth CB, et al. TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo-controlled trial (Basel Thyroid Study). *The Journal of clinical endocrinology and metabolism.* Oct 2001;86(10):4860-4866.

18. Razvi S, Ingoe L, Keeka G, Oates C, McMillan C, Weaver JU. The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function, and quality of life in subclinical hypothyroidism: randomized, crossover trial. *The Journal of clinical endocrinology and metabolism.* May 2007;92(5):1715-1723.

19. Duntas LH, Brenta G. The effect of thyroid disorders on lipid levels and metabolism. *The Medical clinics of North America.* Mar 2012;96(2):269-281.

20. Ladenson PW, Kristensen JD, Ridgway EC, et al. Use of the thyroid hormone analogue eprotirome in statin-treated dyslipidemia. *The New England journal of medicine.* Mar 11 2010;362(10):906-916.

21. Dorr M, Wolff B, Robinson DM, et al. The association of thyroid function with cardiac mass and left ventricular hypertrophy. *The Journal of clinical endocrinology and metabolism.* Feb 2005;90(2):673-677.

22. Biondi B, Palmieri EA, Lombardi G, Fazio S. Effects of subclinical thyroid dysfunction on the heart. *Annals of internal medicine.* Dec 3 2002;137(11):904-914.

23. Gammage MD, Parle JV, Holder RL, et al. Association between serum free thyroxine concentration and atrial fibrillation. *Archives of internal medicine.* May 14 2007;167(9):928-934.

24. Cappola AR, Fried LP, Arnold AM, et al. Thyroid status, cardiovascular risk, and mortality in older adults. *Jama.* Mar 1 2006;295(9):1033-1041.

25. Rodondi N, Bauer DC, Cappola AR, et al. Subclinical thyroid dysfunction, cardiac function, and the risk of heart failure. The Cardiovascular Health study. *Journal of the American College of Cardiology.* Sep 30 2008;52(14):1152-1159.

26. Gencer B, Collet TH, Virgini V, et al. Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. *Circulation.* Aug 28 2012;126(9):1040-1049.

27. Nanchen D, Gussekloo J, Westendorp RG, et al. Subclinical thyroid dysfunction and the risk of heart failure in older persons at high cardiovascular risk. *The Journal of clinical endocrinology and metabolism.* Mar 2012;97(3):852-861.

28. Selmer C, Olesen JB, Hansen ML, et al. Subclinical and overt thyroid dysfunction and risk of all-cause mortality and cardiovascular events: a large population study. *The Journal of clinical endocrinology and metabolism.* Jul 2014;99(7):2372-2382.

29.	Zhang Y, Chang Y, Ryu S, et al. Thyroid hormones and mortality risk in euthyroid individuals: the Kangbuk Samsung health study. *The Journal of clinical endocrinology and metabolism.* Jul 2014;99(7):2467-2476.
30.	Collet TH, Gussekloo J, Bauer DC, et al. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. *Archives of internal medicine.* May 28 2012;172(10):799-809.
31.	Pereg D, Tirosh A, Elis A, et al. Mortality and coronary heart disease in euthyroid patients. *The American journal of medicine.* Aug 2012;125(8):826 e827-812.
32.	Tseng FY, Lin WY, Lin CC, et al. Subclinical hypothyroidism is associated with increased risk for all-cause and cardiovascular mortality in adults. *Journal of the American College of Cardiology.* Aug 21 2012;60(8):730-737.
33.	Volzke H, Robinson DM, Schminke U, et al. Thyroid function and carotid wall thickness. *The Journal of clinical endocrinology and metabolism.* May 2004;89(5):2145-2149.
34.	Biondi B, Wartofsky L. Combination treatment with T4 and T3: toward personalized replacement therapy in hypothyroidism? *The Journal of clinical endocrinology and metabolism.* Jul 2012;97(7):2256-2271.
35.	Pearce EN. Update in lipid alterations in subclinical hypothyroidism. *The Journal of clinical endocrinology and metabolism.* Feb 2012;97(2):326-333.
36.	Bakker SJ, ter Maaten JC, Popp-Snijders C, Slaets JP, Heine RJ, Gans RO. The relationship between thyrotropin and low density lipoprotein cholesterol is modified by insulin sensitivity in healthy euthyroid subjects. *The Journal of clinical endocrinology and metabolism.* Mar 2001;86(3):1206-1211.