Published in final edited form as:

Am Heart J. 2014 January ; 167(1): . doi:10.1016/j.ahj.2013.10.012.

Relation of Hypothyroidism and Incident Atrial Fibrillation (from the Framingham Heart Study)

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Abstract

Background—Hyperthyroidism has a well-described association with atrial fibrillation (AF). However, the relation of hypothyroidism to AF has had limited investigation. Hypothyroidism is associated with cardiovascular risk factors, subclinical cardiovascular disease and overt cardiovascular disease, all of which predispose to AF. We investigated 10-year incidence of AF in a community-dwelling cohort.

Methods—Among 6,653 Framingham heart Study participants, 5,069 participants, 52% woman, mean age 57±12, were eligible after excluding those with missing thyroid stimulating hormone (TSH), TSH <0.45 μU/L (hyperthyroid), TSH >19.9 μU/L or prevalent AF. TSH was categorized by range (0.45 to <4.5, 4.5 to <10.0, 10.0 to 19.9 μU/L) and by quartiles. We examined the associations between TSH and 10-year risk of AF using multivariable-adjusted Cox proportional hazards analysis.

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Disclosures

Dr. Massaro has relation to Cardiovascular Clinical Sciences, Abbott Vascular, Cordis, Medtronic, Merck, and Harvard Clinical Research Institute. None of the other authors report any potential conflicts of interest.

Results—Over 10-year follow-up, we observed 277 cases of incident AF. A 1-standard deviation (SD) increase in TSH was not associated with increased risk of AF (hazard ratio 1.01, 95% confidence interval 0.90 to 1.14, $p=0.83$). In categorical analysis, employing TSH 0.45 to <4.5 $\mu\text{U/L}$ as the referent (equivalent to euthyroid state), we found no significant association between hypothyroidism and 10-year AF risk. Comparing the highest ($2.6 < \text{TSH} < 19.9$ $\mu\text{U/L}$) to lowest ($0.45 < \text{TSH} < 1.3$ $\mu\text{U/L}$) quartiles of TSH further did not identify a significant association between TSH levels and 10-year risk of AF.

Conclusions—In conclusion, we did not identify a significant association between hypothyroidism and 10-year risk of incident AF in a community-based study.

Keywords

Atrial fibrillation; hypothyroidism; risk factors; cohort study

Thyroid hormone dysfunction has been associated with increased incidence of AF and cardiovascular mortality.^{1–7} Prospective community-based studies have demonstrated that hyperthyroidism has greater than a 2-fold increased association with AF compared to the euthyroid state.^{8,9} Over a median 8-year follow-up, the Rotterdam Study found that thyroid function at the upper range of normal was associated with an increased risk of AF.³ In contrast, whether hypothyroidism has a similar association with AF has had limited investigation. Hypothyroidism is associated with multiple cardiovascular risk factors, subclinical and overt cardiovascular disease, all of which have been related to AF. We hypothesized that hypothyroidism would be associated with increased 10-year risk of incident AF in the Framingham Heart Study.

Methods

The Framingham Heart Study was initiated in 1948 to examine cardiovascular disease and its risk factors. The study enrolled community-dwelling participants, termed the Original cohort ($n=5,209$), who have undergone examinations every 2 years.¹⁰ In 1971, the study enrolled the Original cohort's children and their spouses, termed the Offspring cohort ($n=5,124$), who have had examinations every 4 to 8 years.¹¹ The present study used data from Original cohort examination 15 (1977–1979), and Offspring cohort examination 4 (1987–1991). These examinations served as the baseline in the present study. TSH and all covariates including age were defined at this baseline examination for the present analysis.

A total of 6,653 Framingham Heart Study participants were included in these examinations. Participants were excluded from the present analysis for missing thyroid stimulating hormone (TSH) measurement ($n=955$); serum TSH <0.45 $\mu\text{U/L}$, equivalent to hyperthyroidism ($n=372$); serum TSH >19.9 $\mu\text{U/L}$, equivalent to severe hypothyroidism ($n=51$); missing essential covariates ($n=86$); multiple TSH values ($n=2$); prevalent AF ($n=117$); or incomplete follow-up ($n=1$). Participants provided written informed consent at each examination. Study protocols and all examination cycles were approved by the Boston University Medical Center Institutional Review Board.

Participants underwent a physician-administered medical interview, history and examination. Concentrations of TSH values were measured on fasting, morning samples using 2 different assays. In brief, serum samples were stored and then measured from 1981 through 1983 using radioimmunoassay (Diagnostic Products, Los Angeles, CA) and subsequently chemoluminescence assay (London Diagnostics, Eden Prairie, MN) in 1990 and 1991. Details of the TSH assay were described previously.^{9,12} Covariates were selected primarily for their association with AF in prior analyses and included age, sex, body mass index, systolic blood pressure, treatment for hypertension, PR interval, significant murmur

($\geq 3/6$ systolic murmur or any diastolic murmur), tobacco use, and prevalent cardiovascular disease (CVD). CVD is an adjudicated outcome in the Framingham Heart Study and comprised of congestive heart failure, MI (recognized or unrecognized), stroke, and transient ischemic attack.¹³ Further adjustment included use of thyroid medications.

Atrial fibrillation was diagnosed by the presence of AF or atrial flutter on electrocardiogram or Holter monitoring obtained during a Framingham Heart Study clinic visit, an external clinician visit, hospitalization, or review of medical records. Incident AF was adjudicated by 2 Framingham Heart Study cardiologists. Individuals were followed for 10 years or to the development of AF or death.

We summarized data by examining TSH distributions numerically. TSH was natural log transformed as the distribution was skewed. We modelled TSH as a continuous measure, categorically (0.45 to <4.5, 4.5 to <10.0, 10.0–19.9 $\mu\text{U/L}$)^{4,7} and by quartiles. We determined the incidence rate for AF by assessing the number of events per 1000 person-years for each TSH category. The association between 1-standard deviation (SD) TSH and incident AF was evaluated by 10-year Cox proportional hazards regression analysis after censoring for death and adjusting for covariates. Similar analyses were conducted for TSH categories and quartiles. The proportional hazards assumption was held for all models. All analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC). We considered a two-sided $p < 0.05$ as statistically significant. We adhered to the STROBE guidelines.¹⁴ No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Results

Following exclusions, the study cohort consisted of 5,055 Framingham Heart Study participants (52% woman, mean age 57 ± 12) as summarized in Table I. The median year of follow-up was 10 years (SD 2.05). We observed 277 incident AF events up to 10-years during follow-up. Table II describes the multivariable-adjusted incidence rate of AF per TSH categorical range and TSH quartile.

Table III describes the relation of TSH to 10-year risk of AF. A 1-SD increase in TSH was not associated with increased risk of incident AF (hazard ratio [HR] 1.01, 95% confidence interval [CI] 0.90 to 1.14, $p = 0.83$) in multivariable analysis adjusted for age, sex, body mass index, systolic blood pressure, treatment for hypertension, significant murmur ($\geq 3/6$ systolic murmur or any diastolic murmur), prevalent cardiovascular disease (CVD), PR interval, tobacco use, and use of thyroid medications. We found no significant association between hypothyroidism and 10-year AF risk employing TSH by categorical range or quartile. When we performed an interaction analysis, there was no significant interaction of the relation of TSH to atrial fibrillation by age or sex ($p = 0.23, 0.21$ respectively).

Conclusions

The current study did not identify a statistically significant relation between hypothyroidism and incident AF in a prospective, community-based cohort. We had hypothesized that hypothyroidism would increase the risk of AF. Our hypothesis was based on the known relations between cardiovascular risk factors, subclinical and overt cardiovascular disease and hypothyroidism.^{2,15}

We considered that relating hypothyroidism to incident AF merited investigation for several reasons. First, hypothyroidism is associated with multiple cardiovascular risk factors for AF including obesity, systolic blood pressure, diabetes and inflammation.^{16,17} Population-based

studies have demonstrated the relation of increased body mass index to TSH.¹⁸ Hypothyroidism has similarly been related to increased systolic blood pressure^{19,20} and to diabetes mellitus.²¹ Inflammation has been associated with AF in diverse studies,^{17,22} and inflammatory biomarkers such as C-reactive protein are elevated in hypothyroidism.²³

Secondly, hypothyroidism may increase AF risk through subclinical and clinical cardiovascular diseases.^{5–7} Cardiac imaging studies have identified increased left ventricular mass and myocardial stiffness in hypothyroidism,^{24,25} and these may increase risk for AF.¹³ Risk of heart failure is increased in hypothyroidism via multiple mechanisms.^{4,26} In addition, population-based studies have reported an increased prevalence of aortic atherosclerosis and myocardial infarction in subclinical hypothyroidism.^{5,27}

The investigation of hypothyroidism and AF has had contrasting results. Cardiovascular Health Study investigators found that subclinical or overt hypothyroidism was not related to increased incidence of AF.² In contrast, a large Danish registry reported that hypothyroidism was significantly associated with decreased rates of incident AF compared to the euthyroid referent category.²⁸ Our study also showed a trend for lower risk of AF in higher TSH group although it was statistically insignificant and the finding should be interpreted with caution due to a small event number in higher TSH group. In comparison, our 10-year follow-up was longer but our study size was less than the Danish registry analysis (median 5.5 years; n=586,460).

Chief strengths of our study are that we employed a moderate-sized cohort with reliable TSH measurement and robust covariate ascertainment. Limitations include that the sample consisted of middle-age and older adults of European descent, limiting generalizability to other ethnicities and younger individuals. Second, our evaluation of thyroid dysfunction was limited, as we lacked the ability to classify overt or subclinical hypothyroidism with comprehensive thyroid measures. We also used two different thyroid assays that may lead to subtle discrepancy in values. Thyroid levels may additionally fluctuate depending on metabolic parameters that were not included in our analysis. However, we would expect that the resulting misclassification from thyroid measurements would be non-differential with respect to AF and bias our results towards the null. Similarly, we did not construct thyroid measurements as time-dependent covariates. Third, we are unable to classify AF as paroxysmal, persistent, or permanent AF. The relation of thyroid levels to the subtypes of AF and atrial flutter requires continued investigation. Fourth, our cohort may have included participants with AF that was not ascertained by Framingham Heart Study review. We again expect that such misclassification would be non-differential with respect to the exposure. Fifth, we were unable to identify or exclude participants using medications (e.g. amiodarone, lithium, or glucocorticoids) that may alter TSH quantification. Finally we had a limited number of events for incident AF. A study with higher number of events may have improved statistical power to detect the association between hypothyroidism and AF.

Our study did not demonstrate an association between hypothyroidism and increased AF risk in a community-based cohort. Neither did our analysis demonstrate that hypothyroidism is associated with reduced risk of AF, as suggested by recent data.²⁸ Continued investigation in larger cohorts with more events may further clarify the association between hypothyroidism and AF.

Acknowledgments

Grant Support

This work is funded by the American Heart Association (Dr. Magnani: Award # 09FTF2190028) and the NIH (6R01-NS17950 and N01-HC25195; Dr. Benjamin: HL092577, RO1AG028321, RC1-HL101056,

1R01HL102214). This work is partially supported by the Evans Center for Interdisciplinary Biomedical Research ARC on “Atrial Fibrillation at Boston University” (<http://www.bumc.bu.edu/evanscenteribr/>)

Dr. Magnani is supported by American Heart Association award 09FTF2190028 and a Boston University School of Medicine Career Investment Award. This work was supported by NIH grants from the NIH HL092577, RO1AG028321, RC1-HL01056, 1R01HL102214, 6R01-NS17950 and N01-HC25195.

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Table I

Characteristics of study participants

	All (N=5,069)	TSH 0.45–4.5 (N=4,703)	TSH 4.5–10.0 (N=268)	TSH 10.0–19.9 (N=98)
Age (years)	57 ± 12	57 ± 12	62 ± 12	63 ± 11
Women, %	2,635 (52.0)	2,376 (50.5)	187 (69.8)	72 (73.5)
Body mass index (kg/m ²)	26.7 ± 4.6	26.7 ± 4.6	27.1 ± 4.8	27.0 ± 4.8
Systolic blood pressure (mm Hg)	130 ± 19	130 ± 19	133 ± 19	133 ± 19
Hypertension treatment	1,167 (23.0)	1,061 (22.6)	78 (29.1)	28 (28.6)
PR interval duration (ms)	165 ± 25	165 ± 25	168 ± 24	166 ± 26
Significant murmur [†]	137 (2.7)	120 (2.6)	11 (4.1)	6 (6.1)
Prevalent CVD [‡]	580 (11.4)	530 (11.3)	34 (12.7)	16 (16.3)
Current tobacco use	1,330 (26.2)	1,258 (26.7)	50 (18.7)	22 (22.4)
Thyroid medication	123 (2.4)	102 (2.2)	15 (5.6)	6 (6.1)
log _e TSH	0.58 ± 0.63	0.47 ± 0.49	1.82 ± 0.22	2.61 ± 0.19

*
TSH (mIU/L)

Data presented as mean ± standard deviation or n (%).

[†] Significant murmur was defined as at least grade 3 out of 6 systolic or any diastolic murmur.

[‡] Congestive heart failure, MI (recognized or unrecognized) and stroke or transient ischemic attack.

Table II

Incidence of AF according to TSH by range and quartile.

	Total events	Total person-years	Incidence rate per 1000 person-years (95% CI)
TSH range (mIU/L)			
0.45 to <4.5	254/4,703	43,443.6	5.85 (5.13, 6.57)
4.5 to <10.0	19/268	2,383.5	7.97 (4.39, 11.60)
10.0 to 19.9	4/98	907.1	4.41 (0.09, 8.73)
TSH Quartile			
Quartile 1 (0.45 – 1.29)	66/1,395	12,903.5	5.11 (3.88, 6.35)
Quartile 2 (1.30 – 1.79)	63/1,209	11,235.2	5.61 (4.22, 6.99)
Quartile 3 (1.80 – 2.59)	67/1,249	11,570.3	5.79 (4.40, 7.18)
Quartile 4 (2.60 – 19.9)	81/1,216	11,025.2	7.35 (5.75, 8.95)
Total	277/5,069	46,734.2	5.93 (5.23, 6.63)

AF indicates atrial fibrillation; TSH, thyroid stimulating hormone.

Table III

Relation of TSH to 10-year risk of AF.

	HR (95% CI)	P Value
Per standard deviation of log_eTSH		
Age-and sex-adjusted	1.02 (0.91–1.14)	0.71
Multivariable-adjusted*	1.01 (0.90–1.14)	0.83
Per TSH category (mIU/L)*		
0.45 to <4.5 (referent)	-	
4.5 to <10.0	1.23 (0.77–1.97)	0.39
10.0 to 19.9	0.57 (0.21–1.54)	0.27
Per TSH Quartile*		
Quartile 1 (referent)	--	--
Quartile 2	1.08 (0.76–1.54)	0.65
Quartile 3	1.14 (0.80–1.60)	0.47
Quartile 4	1.23 (0.88–1.71)	0.22

* Adjusted for age, sex, body mass index, hypertension treatment, significant cardiac murmur, prevalent cardiovascular disease, PR interval, smoking, and use of thyroid medications. TSH indicates thyroid stimulating hormone; AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio.