Normal Thyroid Function and the Risk of Atrial Fibrillation: the Rotterdam Study

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Context: Hyperthyroidism is an established risk factor for atrial fibrillation (AF), but information concerning the association with variations within the normal range of thyroid function and subgroups at risk is lacking.

Objective: This study aimed to investigate the association between normal thyroid function and AF prospectively and explore potential differential risk patterns.

Design, Setting, and Participants: From the Rotterdam Study we included 9166 participants ≥ 45 y with TSH and/or free T_4 (FT_4) measurements and AF assessment (1997–2012 median followup, 6.8 y), with 399 prevalent and 403 incident AF cases.

Main Outcome Measures: Outcome measures were 3-fold: 1) hazard ratios (HRs) for the risk of incident AF by Cox proportional-hazards models, 2) 10-year absolute risks taking competing risk of death into account, and 3) discrimination ability of adding FT_4 to the CHARGE-AF simple model, an established prediction model for AF.

Results: Higher FT_4 levels were associated with higher risks of AF (HR 1.63, 95% confidence interval, 1.19–2.22), when comparing those in the highest quartile to those in lowest quartile. Absolute 10-year risks increased with higher FT_4 in participants ≤65 y from 1–9% and from 6–12% in subjects ≥ 65 y. Discrimination of the prediction model improved when adding FT_4 to the simple model (c-statistic, 0.722 vs 0.729; $P = .039$). TSH levels were not associated with AF.

Conclusions: There is an increased risk of AF with higher FT_4 levels within the normal range, especially in younger subjects. Adding FT_4 to the simple model slightly improved discrimination of risk prediction. **(*J Clin Endocrinol Metab* 100: 3718–3724, 2015)**

Atrial fibrillation (AF) is the most common cardiac arrhythmia and a leading cause of cardiovascular disease, particularly stroke (1). Lifetime risks for developing AF in Europe are calculated to be up to 25% (2). Despite efforts to improve management of major classical risk factors of AF (eg, hypertension), prevalence and costs of AF are expected to increase in upcoming years (3, 4). This highlights the need to improve prevention of AF and identify additional risk factors. Overt and subclinical hyperthyroidism are well-documented risk factors for AF, with a prevalence of AF of over 10% in patients with hyperthyroidism (5–7). Furthermore, higher TSH levels within the normal range have been associated with increased cardiovascular mortality and an unfavorable metabolic profile (8), whereas low-normal TSH levels are associated with increased risks of fractures and depressive disorders

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Abbreviations: AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; ECG, electrocardiogram; FT_4, free T_4; HR, hazard ratio; MEANS, Modular ECG Analysis System; MI, myocardial infarction; NRI, Net Reclassification Index; RS, Rotterdam Study; RSI, RS Cohort 1; RSII, RS Cohort 2; RSIII, RS Cohort 3; TPOAb, thyroid peroxidase antibodies.

(8, 9). Nevertheless, only two studies have specifically investigated the association between thyroid function in the normal range and AF (10, 11) and both had specific limitations. Neither addressed possible differential risks in specific subgroups (eg, sex) or possible clinical implications. Identification of specific populations at risk is a crucial requirement in a primary prevention setting or with a targeted screening approach. Therefore, we aimed to investigate the association between variations in normal thyroid function and AF in a longitudinal prospective cohort study, to explore possible subgroups at risk and calculate absolute 10-year risk of AF. Furthermore, we assessed the potential role of thyroid function in a risk prediction model for AF.

Materials and Methods

Study population

The Rotterdam Study (RS) is a prospective cohort study, ongoing since 1990, in Ommoord, a suburb of the city of Rotterdam, The Netherlands. The study targets cardiovascular, endocrine, hepatic, neurologic, ophthalmic, psychiatric, dermatological, oncological, and respiratory disease. As of now now, 14 926 subjects of 45 years and older are included in the RS. The participants are interviewed at home and extensively examined at the research center at baseline. These examinations focused on possible causes of diseases in the middle-aged and elderly. Participants of the RS are followed for several older age–related diseases. The aims and design of the RS have been described in detail elsewhere (12). For this study we included participants from three independent cohorts within RS: RS Cohort 1 (RSI), including 7983 participants age at least 55 years (baseline, 1990–1993), RS Cohort II (RSII), including 3011 participants age at least 55 years (baseline, 2000–2001), and RS Cohort 3 (RSIII), including 3932 participants age at least 45 years (baseline, 2006–2008). Participants from the three cohorts were eligible for the study if TSH or FT_4 measurements were performed and if information on AF was available. All study participants were followed up from the day of baseline laboratory testing to date of onset of AF, to death, or to June 1, 2012, whichever came first. The Medical Ethics Committee of the Erasmus University has approved study protocols, and written informed consent was obtained from all study participants.

Assessment of thyroid function

Thyroid function was measured using the same methods and assay in all samples, which were collected between 1997 and 2008, depending on the cohort. TSH, free T4 (FT_4), and thyroid peroxidase antibodies (TPOAb) measurements were performed in serum samples stored at −80°C (The electrochemiluminescence immunoassay for FT_4, TSH, and TPOAb, "ECLIA," Roche). Date and time of blood drawing was recorded and regarded as baseline. We determined cutoff values for normal range TSH as 0.4–4.0 mIU/L and FT_4 as 11–25 pmol/L (0.86–1.94 ng/dL) according to guidelines and previous studies (10). TPOAb levels greater than 35 kU/mL were regarded as positive, according to manufacturer recommendation.

Diagnosis of AF

Ascertainment of AF cases within RS has been reported elsewhere (2). In short, cases of AF, including paroxysmal AF, were ascertained using three methods. Electrocardiograms (ECGs) were recorded at baseline and during follow-up examinations, stored digitally, and analyzed by the Modular ECG Analysis System (MEANS) (13, 14). As verification, all ECGs with a diagnosis of AF, atrial flutter, or any other rhythm disorders by the MEANS program were recoded by 2 independent research physicians who were blinded to MEANS diagnosis. The judgment of a cardiologist was sought and taken as decisive in case disagreement persisted between the coding physicians. In addition, information on AF was obtained for all participants from general practitioners records, which included their own results as well as results from physicians practicing in hospitals and outpatient clinics. Finally, information was obtained from a national registry of all hospital discharge diagnoses. Those patients who developed AF during a serious disease, resulting in death shortly after the detection of AF, which was not the cause of the serious disease, were not considered to have AF and were censored on date of detection of AF. Furthermore, subjects with transitory AF during myocardial infarction (MI) or during cardiac operative procedures were not included among AF cases. We did not distinguish between AF and atrial flutter when identifying cases because the conditions are similar with respect to risk factors and consequences (15, 16).

Baseline measurements

Information on smoking and history of thyroid disease was derived from baseline questionnaires. Systolic and diastolic blood pressure (BP) were calculated as the average of two consecutive measurements. Hypertension was defined as systolic BP at least 140 mm Hg or diastolic BP at least 90 mm Hg or using antihypertensive medication. Cholesterol was measured using standard laboratory techniques. History of diabetes was defined by a repeated impaired fasting glucose at least 7 mmol/L or use of antiglycemic medication. Coronary heart disease (CHD) was defined as a history of MI, percutaneous coronary intervention or coronary artery bypass graft (17). Assessment of heart failure was performed using a validated score (18), according to the definition of heart failure of the European Society of Cardiology (19). This score was based on the presence of at least two signs or symptoms suggestive of heart failure (shortness of breath, ankle swelling and pulmonary crepitations) or use of medication for the indication of heart failure, in combination with objective evidence of cardiovascular disease including angina pectoris, MI, and left ventricular hypertrophy. Furthermore, heart failure cases were identified through hospital and medical records.

Statistical analysis

Details of the statistical analyses performed are included in the Supplemental Material. In short, we performed logistic regression to assess the association between thyroid function and prevalent AF, and Cox proportional-hazards models were used to assess the association between thyroid function and incident AF prospectively. TSH and FT_4 were examined as continuous measures and quartiles. Primary models adjusted for age and sex and multivariable models additionally adjusted for smoking, hypertension, cholesterol, diabetes, and body mass index (BMI). We performed predefined stratification by age categories: cutoff at 65 years of age-, sex, prevalent CHD, and TPOAb positivity.

Absolute 10-year risk probabilities were estimated taking competing risk of death into account (20). To investigate the robustness of our findings, we conducted sensitivity analyses 1) including only those participants included in the previous report on thyroid function and AF from RS (10); 2) including only subjects using thyroid hormone medication; 3) excluding participants with thyroid function–altering medication, including thyroid hormone replacement therapy, antithyroid drugs, amiodarone, and corticosteroids at baseline; 4) excluding participants with thyroid function altering–medication at baseline and followup; and 5) excluding the first 2 and first 4 years of followup to examine possible reverse causality. Furthermore, we compared discrimination of two prediction models by using C-statistic and Net Reclassification Index (NRI). The first model, proposed in 2013 by the CHARGE-AF Consortium, will be referred to as the Simple Model (21) (Supplemental Material). The second model additionally included FT_4 in the full and normal range. For these analyses we excluded all nonwhite participants (n = 357). The reclassification tables classified participants in AF risk categories of low (<2.5%), intermediate (2.5–5%), and high (>5%) (21). Statistical analyses were performed using SPSS version 21 (SPSS IBM), R statistical software (survival, cmprsk, and nricens packages; R-project, Institute for Statistics and Mathematics, R Core Team, version 3.0.2) or Stata (StataCorp; Stata Statistical Software: Release 13; StataCorp LP).

Table 1. Baseline Characteristics of Included Participants (n = 9166)

Variable	n (%)[d]
Age, y[a]	65.0 (9.9)
Female	5200 (56.7)
History of diabetes	773 (8.4)
BMI kg/m^2 [a]	27.1 (4.1)
Cholesterol mmol/L[a]	5.7 (1.0)
Smoking	
Current	1857 (20.3)
Past	4376 (47.7)
Never	2855 (31.1)
Hypertension	4743 (51.7)
TSH mIU/L[b,c]	1.91 (1.29–2.77)
FT_4 pmol/L	15.7 (2.3)
TPOAb positive (> 35 kU/L)	1200 (13.1)
Use of thyroid medication	256 (2.8)
History of CHD	638 (6.9)

For the survival analyses, 399 participants had prevalent AF and 27 participant did not have follow-up times or data on AF and were excluded, making the total number 8740 participants.

[a] Values are Mean (SD).

[b] Values are Median (IQR)

[c] CHD includes myocardial infarction, coronary, and so on.

[d] Values are number of participants and percentage unless otherwise specified.

Results

In total, 9166 participants were included (mean age, 65 y) in the cross-sectional and 8740 in the longitudinal analyses (399 participants with AF at baseline and 27 with missing follow-up data were excluded) (Table 1). Among included participants, five missed TSH measurement and six FT_4 measurement. Only participants with both TSH and FT_4 measurements available were included in the analyses evaluating the associations within normal ranges. During a median followup of 6.8 years (interquartile range, 3.9–10.9 y) a total of 403 AF events occurred, with an incidence rate of 6.2 per 1000 person-years. There were 256 participants using levothyroxine-replacement therapy, which was prescribed by their own general practitioner or specialist and within the context of regular treatment and blinded to measurements of the RS. Of these, 208 reported a history of hypothyroidism and 40 reported a history another thyroid disease.

Thyroid function and AF

The cross-sectional analyses are shown in Supplemental Table 1. Increased levels of FT_4 were associated with an increased risk of AF for the continuous analysis (odds ratio, 1.21; 95% confidence interval [CI], 1.15–1.28) and for FT_4 quartiles (odds ratio, 2.24; 95% CI, 1.59–3.16, lowest vs highest quartile; *P* for trend < .001). The longitudinal analyses were conducted after excluding subjects with prevalent AF, and comprised 8740 participants (Table 2). The risk of AF was significantly higher with higher levels of FT_4, both outside (hazard ratio [HR], 1.07; 95% CI, 1.03–1.12,) as within the normal range of thyroid function (HR, 1.10; 95% CI, 1.04–1.15) (Table 2). After excluding subjects with TSH and/or FT_4 values outside the reference range and thyroid hormone medication users (n = 1333), participants in the highest quartile compared with the lowest quartile of FT_4 had an increased risk of AF in the multivariable analysis (HR, 1.63; 95% CI, 1.19–2.22; *P* for trend = .005) (Table 2). Additionally adjusting for time of blood drawing, fasting state at blood drawing, prevalent CHD at baseline, or cohort did not alter risk estimates. There was no association between TSH and AF in the cross-sectional or survival analyses (Supplemental Table 1, Table 2).

Stratified and sensitivity analyses

There was a differential risk by age (*P* for interaction = .040) (Table 3). Comparing the highest quartile of FT_4 to the reference quartile in participants below and above 65 years of age there was an increased risk of AF, with HRs of 2.23 (95% CI, 1.18–4.22) and 1.45 (95% CI, 1.01–2.08) respectively (Figure 1, Supplemental Table 2). No differences were found when stratifying for sex, history of CHD, and TPOAb positivity (Supplemental Table 3). Including only the participants analyzed previously in RS (10), risk estimates are more comparable to our current results, with an association between FT_4 (*P* for trend =

Table 2. Association Between Thyroid Function and Incident AF

	Incident AF N	Total N	HR (95% CI) Adjusted for Age and Sex	HR (95% CI) Multivariable Adjustment[b]
TSH mIU/L	402	8736	0.94 (0.84–1.06)	0.91 (0.81–1.03)
FT_4 pmol/L	403	8734	1.06 (1.02–1.10)	1.07 (1.03–1.12)
Within normal function of TSH and FT_4[a], excluding thyroid medication users				
TSH mIU/L	334	7409	0.91 (0.73–1.13)	0.91 (0.73–1.09)
FT_4 pmol/L	334	7409	1.09 (1.03–1.15)	1.10 (1.04–1.15)
TSH quartile				
0.41–1.28	94	1850	1 (Reference)	1 (Reference)
1.29–1.80	88	1858	1.03 (0.77–1.38)	1.04 (0.81–1.39)
1.81–2.48	76	1858	0.90 (0.66–1.22)	0.93 (0.69–1.26)
2.49–3.99	76	1843	0.99 (0.73–1.33)	0.95 (0.70–1.29)
P for trend			.71	.60
FT_4 quartile				
11.01–14.33	64	1862	1 (Reference)	1 (Reference)
14.34–15.59	84	1861	1.22 (0.88–1.70)	1.28 (0.93–1.78)
15.60–16.96	80	1861	1.18 (0.85–1.63)	1.20 (0.86–1.66)
16.97–24.69	106	1825	1.56 (1.14–2.12)	1.63 (1.19–2.22)
P for trend			.008	.005

TSH was log transformed for the continuous analyses, and results are per one increase of the natural logarithm of TSH. Five participants had missing TSH and six had missing FT_4 values. No thyroid function measurements were missing in the normal range analyses.

[a] Normal range of TSH, 0.4–4.0 mIU/L and of FT_4, 11–25 pmol/L (conversion, 1 pmol/L = 0.0777 ng/dL).

[b] Adjusted for age, sex, BMI, smoking, hypertension, diabetes and cholesterol.

.001) and AF but not for TSH (*P* for trend = .32). Including only thyroid hormone users with thyroid function in normal range (n = 720; events = 12), also yielded higher risks for FT_4, but did not reach statistical significance (HR, 1.07; 95% CI, 0.88–1.31). Excluding participants with thyroid function–altering medication and excluding the first 2 or 4 years of followup, did not alter risk estimates (Supplemental Table 4).

Absolute risk calculation and prediction models

Absolute 10-year risks of AF were plotted against FT_4 serum values within the normal range in Figure 2 for both age groups (< 65 and ≥ 65 y). The 10-year absolute risk for those older than 65 years gradually increased from 6% up to 12%. For younger participants, risk increased from 1% to almost 9%. Adding FT_4 to the Simple Model slightly improved discrimination of the model (C-statistic, 0.722 vs 0.729; *P* = .039; Table 4). Supplemental Tables 5 and 6 summarize the NRI results when adding FT_4 to the Simple Model. There was no significant improvement in NRI for the full or normal range of FT_4.

Discussion

Higher FT_4 levels (within the normal range) are associated with an increased risk of AF, irrespective of age, sex, and other potential confounders, with consistent results for both prevalent and incident AF. This effect was stronger among subjects younger than 65 years of age. We found higher 10-year absolute risks with increasing FT_4 levels in participants older than 65 years of age with an increase in risk from 6–12%. In younger participants this was more marked, with an increase of risk from 1–9% with increas-

Table 3. Stratified Analysis for TSH and FT_4 Within Normal Range and Incident AF

Stratification	Incident AF	AF N	Total N	HR (95% CI) Adjusted for Age and Sex	*P* Value	HR (95% CI) Multivariable Adjustment[a]	*P* Value
TSH mIU/L							
	<65 y	82	4273	0.80 (0.51–1.26)	.34	0.83 (0.53–1.31)	.43
	≥ 65 y	252	3136	0.94 (0.73–1.20)	.59	0.93 (0.72–1.19)	.55
P for interaction				.54		.46	
FT_4 pmol/L							
	<65 y	82	4273	1.19 (1.08–1.32)	<.001	1.19 (1.07–1.32)	.001
	≥ 65 y	252	3136	1.06 (1.00–1.12)	.071	1.06 (1.00–1.13)	.046
P for interaction				.059		.040	

Normal range of TSH, 0.4–4.0 mIU/L and of FT_4, 11–25 pmol/L (conversion, 1 pmol/L = 0.0777 ng/dL), excluding thyroid hormone users. TSH was log transformed for the continuous analyses, results are per one increase of the natural logarithm of TSH.

[a] Adjusted for age, sex, BMI, smoking, hypertension, diabetes, and cholesterol.

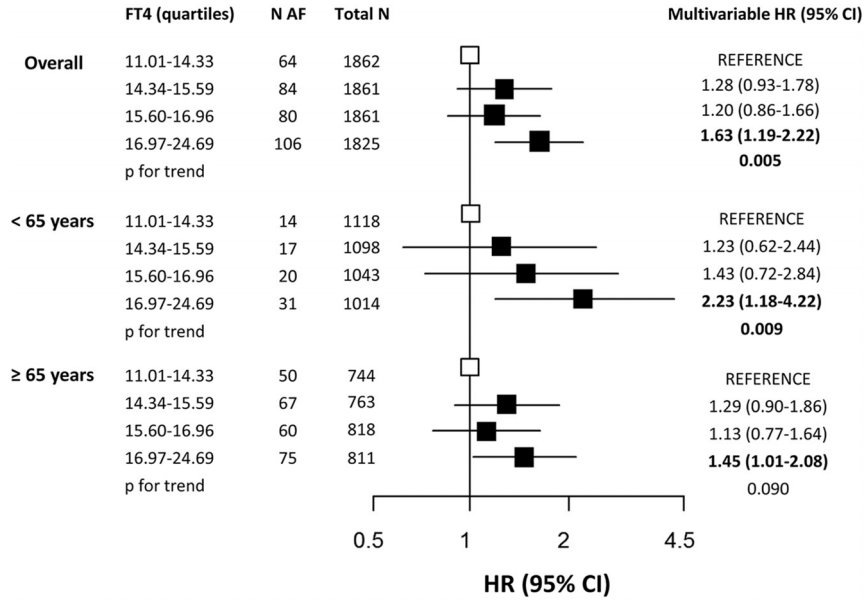

Figure 1. Stratified analysis for the association between FT_4 levels in normal range and incident AF. The normal range of TSH was defined as 0.4–4.0 mIU/L and of FT_4 as 11–25 pmol/L (conversion, 1 pmol/L = 0.0777 ng/dL), thyroid hormone medication users were excluded. The multivariable analyses were adjusted for age, sex, BMI, smoking, hypertension, diabetes and cholesterol.

ing FT_4 levels within the normal range. Adding FT_4 to the Simple Model for AF risk prediction improved discrimination of the model slightly.

Our overall results concerning relative risks are consistent with a previous study by Selmer et al (7) that reported a higher risk of AF toward hyperthyroidism. Our results are also in line with two previous studies that focused on normal thyroid function and AF (10, 11). The population-based study by Cappola et al (11) (2843 participants > 65 years) found an increased risk with higher FT_4 levels, within the normal range of thyroid function. This study, however, had a mean participant age of almost 75 years and did not include younger participants. Furthermore, it did not provide information on potential absolute risks, differential risks, or on the predictive ability of FT_4 for AF.

A previous report from the RS including only 1426 participants, reported an increased risk with high-normal thyroid function (10) with an association between TSH levels and an increased risk of AF and a graded nonsignificant association with FT_4. Our study shows that the associated risks are mainly with increased FT_4 levels and not with TSH. Potential explanations for differences between previous and current report from the RS include population size (1426 vs 8740 participants), lack of subgroup analyses in the previous report, follow-up period, and different characteristics of the study population. In the previous study, the included participants were slightly older at baseline (68.4 vs 65.0 y), less AF events had occurred (n = 105 vs 334) and followup started more than 10 years earlier. A sensitivity analysis including only participants of this earlier study, with updated number of events and follow-up time showed results comparable to the findings of the current study, ie, without an association with TSH but with an increased risk of AF with increased FT_4 levels.

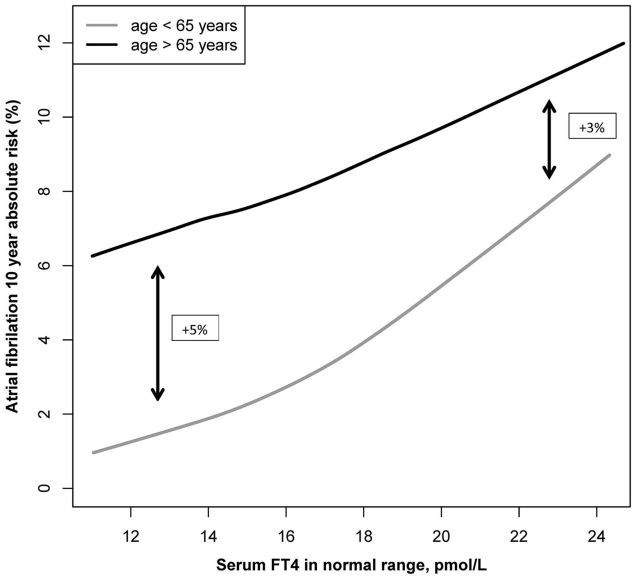

Figure 2. AF absolute 10-year risk for euthyroid subjects below and above 65 years of age plotted against FT_4 within the normal range. The normal range of FT_4 was defined as 11–25 pmol/L (conversion, 1 pmol/L = 0.0777 ng/dL). Absolute risk analyses were conducted taking competing risk of death into account using a Fine and Gray model and adjusted for age and sex within strata.

Thyroid hormones are known to have numerous direct effects on the cardiovascular system, including altering gene expression of several cardiac genes (22), decreasing systemic vascular resistance (23) and altering systolic and diastolic cardiac function (24, 25). Thyroid hormone bioactivity is determined by the binding of the metabolically active form of T_3 to its nuclear receptors, which function as transcription factors modulating gene expression. However, FT_4 is the predominant marker of thyroid hormone in serum and important for the negative feedback mechanism. The level of serum FT_4 is tightly regulated by the hypothalamic-pituitary-thyroid axis, with a different set point for each individual (26, 27), which is under strong genetic influence (28). This could explain why even within the normal range of thyroid function, defined mostly by TSH, there is an increased risk of AF with higher

Table 4. Discriminative Ability Adding FT_4 to CHARGE-AF Simple Model for 10 yr Risk Prediction of Incident AF

Participants	C-Statistic Simple Model	C-Statistic Simple Model including FT_4	*P* Value
All participants	0.722	0.729	.039
Normal range[a]	0.722	0.730	.071
Age < 65 y	0.694	0.712	.132
Age ≥ 65 y	0.677	0.683	.299

CHARGE-AF Simple model included age, race, height, weight, BP, smoking, anti-hypertensive medication use, diabetes, history of heart failure, and history of MI. For these analyses we excluded all nonwhite participants. Age-stratified analyses included age as a predictor.

[a] Normal range of TSH, 0.4–4.0 mIU/L and FT_4, 11–25 pmol/L (conversion, 1 pmol/L = 0.0777 ng/dL), excluding thyroid hormone users.

FT_4 levels. We find a higher risk of AF in both younger as well as older participants. However, in the younger participant group, this risk seems stronger. One explanation could be a changed set point among the elderly compared with younger participants. The individual set point can be modulated by several pathophysiological as well as physiological processes such as aging (29). Therefore, the same values of thyroid function serum makers may hypothetically have different effects in younger vs older participants, especially over time. However, pathways possibly leading to the differences between different age groups still must be determined and further explored.

The results of this study could have several implications. Currently, the normal range of thyroid function is defined biochemically, which is solely based on the measurement itself rather than on adverse clinical outcomes related to these measurements. It has therefore been debated whether the currently applied reference ranges should be redefined (30, 31). Our study provides evidence that variations within the reference range are associated with AF. Future studies should confirm these results and investigate whether variations within the reference range currently applied are associated with other cardiovascular outcomes.

The prevalence of AF and its burden on health care is increasing despite efforts to control risk factors (2, 4). Acknowledging nonclassical risk factors might aid in the recognition and decision making concerning AF. With this study we show that even high-normal thyroid function has implications on relative risks, absolute risks, and prediction of developing AF and perhaps should be taken into account in further research concerning risk prediction or screening of AF.

In recent years, the proportion of people treated for subclinical hypothyroidism has increased (32), mostly in an attempt to prevent possible adverse effects on the cardiovascular system. However, our results could suggest that treatment of subclinical hypothyroidism is not without danger and even when thyroid function is biochemically well controlled, there can still be an increased risk of AF. Including only thyroid hormone users within the normal range of thyroid function shows a similarly increased risk in higher FT_4 level, even though not significant due to low power in this specific subgroup. Population-based studies have shown that among patients treated with thyroid medication, more than one fifth have TSH levels suppressed below normal. Future studies should determine whether the increased risk of AF is also applicable for those with high-normal thyroid hormone values due to replacement therapy.

A major strength of our study is the inclusion of a large number of participants in a population-based cohort and with longitudinal ascertainment of a large number of AF events. This allowed investigation of possible differential risks in several subgroups and calculation of absolute risks. Other strengths are the extensive evaluation and case finding of participants with AF, both at baseline as well as during followup and ability to adjust for a wide variety of confounders. A limitation of our study is that despite this amount of variables included in the analyses, residual confounding cannot be excluded. Measurements of total T_3 and free T_3 are not available in the RS and therefore the association between these thyroid function markers and AF could not be assessed. Also, we measured thyroid function only at baseline and therefore could not take changes in thyroid function into account, which is a limitation for most previous studies in this field (33, 34). Furthermore, this study is conducted in a mainly white population of 45 years and older and may not be generalizable to other populations.

Conclusions

There is an increased risk of AF with higher FT_4 levels in the normal range of thyroid function. There is a trend of higher absolute risk increases with increasing FT_4 levels from 1% to 9% in those younger than 65 years of age and from 6–12% in older participants. This suggests caution in decision making regarding intensity of treatment of subclinical hypothyroidism. Assessing thyroid function, even in the normal range, for risk prediction of AF development should be further investigated.

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