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# Thyroid Function Within the Normal Range, Subclinical Hypothyroidism, and the Risk of Atrial Fibrillation

Editorial, see p 2117

Christine Baumgartner, MD  
et al

**BACKGROUND:** Atrial fibrillation (AF) is a highly prevalent disorder leading to heart failure, stroke, and death. Enhanced understanding of modifiable risk factors may yield opportunities for prevention. The risk of AF is increased in subclinical hyperthyroidism, but it is uncertain whether variations in thyroid function within the normal range or subclinical hypothyroidism are also associated with AF.

**METHODS:** We conducted a systematic review and obtained individual participant data from prospective cohort studies that measured thyroid function at baseline and assessed incident AF. Studies were identified from MEDLINE and EMBASE databases from inception to July 27, 2016. The euthyroid state was defined as thyroid-stimulating hormone (TSH) 0.45 to 4.49 mIU/L, and subclinical hypothyroidism as TSH 4.5 to 19.9 mIU/L with free thyroxine (fT4) levels within reference range. The association of TSH levels in the euthyroid and subclinical hypothyroid range with incident AF was examined by using Cox proportional hazards models. In euthyroid participants, we additionally examined the association between fT4 levels and incident AF.

**RESULTS:** Of 30 085 participants from 11 cohorts (278 955 person-years of follow-up), 1958 (6.5%) had subclinical hypothyroidism and 2574 individuals (8.6%) developed AF during follow-up. TSH at baseline was not significantly associated with incident AF in euthyroid participants or those with subclinical hypothyroidism. Higher fT4 levels at baseline in euthyroid individuals were associated with increased AF risk in age- and sex-adjusted analyses (hazard ratio, 1.45; 95% confidence interval, 1.26–1.66, for the highest quartile versus the lowest quartile of fT4; *P* for trend  $\leq 0.001$  across quartiles). Estimates did not substantially differ after further adjustment for preexisting cardiovascular disease.

**CONCLUSIONS:** In euthyroid individuals, higher circulating fT4 levels, but not TSH levels, are associated with increased risk of incident AF.

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Sources of Funding, see page 2113

**Key Words:** atrial fibrillation  
■ hypothyroidism ■ thyrotropin  
■ thyroxine

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## Clinical Perspective

### What Is New?

- Subclinical hyperthyroidism is associated with increased risk of atrial fibrillation, but the association with thyroid function in the normal range or subclinical hypothyroidism is unclear.
- We performed an individual participant data analysis investigating the association between thyroid function within the normal range or subclinical hypothyroidism and the risk of atrial fibrillation, including >30 000 participants from 11 prospective cohort studies.
- Our study showed that higher free thyroxine levels were associated with an increased risk of atrial fibrillation in euthyroid persons, whereas thyroid-stimulating hormone levels were not.

### What Are the Clinical Implications?

- Given the high prevalence of atrial fibrillation and its potentially disabling clinical outcomes, identification of modifiable risk factors is important.
- Free thyroxine levels might add to further assessment of atrial fibrillation risk.
- Further studies need to investigate whether these findings apply to thyroxine-treated patients, who often have higher circulating free thyroxine levels than untreated participants, to assess whether treatment goals should be modified.

**A**trial fibrillation (AF) affects >30 million individuals worldwide, and its prevalence and incidence are increasing globally.<sup>1</sup> AF leads to significant morbidity and mortality,<sup>2</sup> and increases the risk of stroke, heart failure, and subsequent hospitalizations.<sup>3</sup> Identification of modifiable risk factors and potentially reversible causes is crucial for the prevention and treatment of AF. Overt hyperthyroidism is a recognized risk factor for AF,<sup>4</sup> and measurement of thyroid function is recommended in the initial evaluation of patients with AF.<sup>5</sup> Subclinical thyroid dysfunction, which is defined as abnormal thyroid-stimulating hormone (TSH) levels with free thyroid hormone concentrations within the reference range, is common, with up to 9% of the adult population being affected by subclinical hypothyroidism and 2% to 3% by subclinical hyperthyroidism.<sup>6,7</sup> The risk of AF is increased in subclinical hyperthyroidism, especially when TSH levels are <0.10 mIU/L.<sup>8,9</sup>

Subclinical hypothyroidism increases the risk of cardiovascular events,<sup>10</sup> but its association with incident AF risk remains uncertain.<sup>9,11–13</sup> Variations in thyroid hormone levels within the reference range have been associated with adverse cardiac events, and recent studies have suggested that higher free thyroxine (fT4) levels lead to an increased risk of heart failure and sudden

cardiac death in euthyroid individuals.<sup>14,15</sup> Data from observational studies on the association between thyroid function within the reference range and the incidence of AF are conflicting.<sup>11,16,17</sup>

Therefore, we aimed to examine the risk of AF in individuals with thyroid function within the normal range and subclinical hypothyroidism by performing an individual participant data (IPD) analysis of prospective cohort studies. An IPD analysis might help clarify the conflicting results of previous studies; it is considered the methodological gold standard for summarizing evidence from observational studies and for analyzing the impact of age, sex, and thyroid medication in subgroup analyses, because it is not affected by potential aggregation bias from study-level meta-analyses (ecological fallacy).<sup>18,19</sup> This approach allows also a uniform definition of thyroid function and adjustments of similar confounders with the aim of reducing heterogeneity across studies.

## METHODS

This IPD analysis was conducted according to the predefined protocol registered on the international prospective register of systematic reviews PROSPERO (registration number CRD42016043906). Reporting conformed to the PRISMA-IPD (Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data) statement.<sup>20</sup>

## Data Sources and Study Selection

We conducted a systematic literature review of published articles in the MEDLINE and EMBASE databases, from inception to July 27, 2016, on the association between TSH and AF events, without language restriction (**Methods I in the online-only Data Supplement**). We also performed a manual literature search, in which we reviewed expert articles in the field, screened bibliographies from retrieved articles, and requested data from cohorts participating in the Thyroid Studies Collaboration.<sup>8,10,21,22</sup> Predefined inclusion and exclusion criteria were used to improve comparability and quality of the studies. We included only full-text published longitudinal cohort studies that assessed thyroid function at baseline (serum TSH and fT4), and that had a euthyroid control group and prospective follow-up of AF events. We excluded studies that included only participants with overt thyroid dysfunction (abnormal TSH and fT4 levels), that included only participants who took thyroid-altering medications (antithyroid drugs, thyroxine, or amiodarone), or that assessed only postoperative AF events. Two authors (C.B. and C.F.) independently screened references for eligibility; discrepancies were resolved in consultation with a third author (N.R.). Agreement between reviewers was 98.6% for the first screening phase (titles and abstracts,  $\kappa=0.66$ ), and 95.0% for the second screening phase (full-text screen,  $\kappa=0.83$ ).

Two authors (C.B. and C.F.) rated the methodological quality of the included studies based on individual criteria of the Newcastle-Ottawa Quality Assessment Scale (**Methods II in the online-only Data Supplement**).<sup>23</sup>

**Table 1. Study Characteristics**

Study	Description of Study Sample	No.*	Age, Median (Range), y†	Women, n (%)	Cardiovascular Disease, n (%)‡
United States					
Cardiovascular Health Study <sup>13</sup>	Community-dwelling adults with Medicare eligibility in 4 US communities	3328	73 (64–98)	1917 (57.6)	845 (25.4)
Health ABC Study <sup>25</sup>	Community-dwelling adults with Medicare eligibility in 2 US communities	2346	74 (69–81)	1143 (48.7)	625 (27.1)
MrOS Study <sup>26</sup>	Community-dwelling men aged ≥65 y in 6 US clinical centers	678	72 (65–91)	0	135 (19.9)
Europe					
Bari Study <sup>27</sup>	Outpatients with heart failure followed up by Cardiology Department in Bari, Italy	268	65 (21–92)	55 (20.5)	103 (38.4)
Leiden 85-plus Study <sup>28</sup>	All adults aged 85 y living in Leiden, the Netherlands	432	85 (85–85)	281 (65.1%)	166 (38.4)
SHIP <sup>29</sup> **	Adults living in Western Pomerania, Germany	2339	45 (20–85)	1191 (50.9)	100 (4.3)
InCHIANTI Study <sup>30</sup>	Community-dwelling adults aged ≥65 y living in Tuscany, Italy	1051	71 (21–103)	581 (55.3)	123 (11.7)
Rotterdam Study <sup>16</sup>	Inhabitants of Ommoord (The Netherlands) aged ≥ 55 y	1607	68 (55–93)	975 (60.7)	412 (25.6)
PROSPER Study <sup>31</sup>	Community-dwelling elderly with high cardiovascular risk in The Netherlands, Scotland, and Ireland	5334	74 (69–83)	2645 (49.6)	2356 (44.2)
EPIC-Norfolk Study <sup>32</sup>	Adults aged 40–79 y living in Norfolk, England	11642	58 (39–78)	6181 (53.1)	442 (3.8)
Australia					
Busselton Health Study <sup>33</sup>	Adults living in Busselton, Western Australia	1060	46 (18–81)	539 (50.9)	54 (5.1)
Overall	11 Cohorts	30085	69 (18–103)	15508 (51.6)	5371 (17.9)
Studies in which IPD were not available					
Framingham Heart Study <sup>9</sup>	Adults aged ≥60 y from Framingham, USA	1759††	≥60 (NA)	1037 (59.0)	NA
Rotterdam Study Cohorts I, II and III <sup>24</sup> ‡‡	Adults aged ≥55 y for Cohort II and ≥45 y for Cohort III from Ommoord, The Netherlands	8740	63 (45–105)	5010 (57.3)	NA

(Continued)

Institutional review boards approved all studies, and written informed consent was granted by all participants. The sponsors had no role in the design, analysis, or reporting of the study.

## Data Extraction

We contacted investigators from included studies and requested prespecified IPD on baseline thyroid function (TSH and fT4), demographic characteristics (age, sex, race), cardiovascular and AF risk factors (blood pressure, diabetes mellitus, total cholesterol, smoking), preexisting cardiovascular disease, history of AF, and medication use at baseline (thyroid-altering medications including thyroxine, antithyroid medication, lithium, amiodarone, glucocorticoids, iodine, aspirin, furosemide; cardiovascular medications such as antihypertensive and lipid-lowering drugs) for each participant (see [Table I in the online-only Data Supplement](#) for definition of baseline covariates in the included studies). Data on AF outcomes were collected. We checked data for consistency and completeness, excluded unrealistic data points, and contacted authors of the cohorts to clarify variable definitions. For 2 studies for which authors

could not share IPD (one cohort because of legal constraints,<sup>24</sup> and another<sup>9</sup> because of prohibitive costs; Table 1), we looked for published aggregate data on the association between thyroid function and AF, so we could perform sensitivity analyses that included these studies.

## Thyroid Function Testing

In line with our previous analyses,<sup>8,10,21</sup> and based on an expert consensus meeting of the Thyroid Studies Collaboration (International Thyroid Conference, Paris, France, 2010), expert reviews,<sup>34,35</sup> and previous large cohorts,<sup>13,36</sup> we used uniform cutoff levels of TSH to define thyroid dysfunction and optimize the comparability of the included studies. Similar to previous studies, euthyroidism was defined as a TSH level from 0.45 to 4.49 mIU/L and further subdivided into 5 categories: 0.45 to 0.99 mIU/L; 1.00 to 1.49 mIU/L; 1.50 to 2.49 mIU/L; 2.50 to 3.49 mIU/L; and 3.50 to 4.49 mIU/L.<sup>37</sup>

Subclinical hypothyroidism was defined as a TSH level between 4.5 and 19.9 mIU/L with fT4 levels in the reference range, and was further subdivided into subclinical hypothyroidism with mildly elevated TSH 4.50 to 6.9 mIU/L, moderately

Table 1. Continued

Endogenous Subclinical Hypothyroidism, n (%) <sup>§</sup>	Medication Users During Follow-up, n (%) <sup>  </sup>		Follow-Up <sup>#</sup>			
	Thyroxine	Antithyroid Medication	Start, y	Duration, Median (IQR), y	Person-Years	AF Events, n (%)
436 (13.1)	308 (9.5)	NA	1994–1995	11.7 (7.0–18.1)	32 632	886 (26.6)
270 (11.5)	114 (4.9)	2 (0.1)	1997	8.1 (7.4–8.3)	16 155	201 (8.6)
45 (6.6)	18 (2.7)	0	2000–2002	12.6 (11.2–13.1)	7668	62 (9.1)
23 (8.6)	22 (8.2)	8 (3.0)	2006–2008	1.3 (0.6–1.9)	339	14 (5.2)
27 (6.3)	5 (1.2)	3 (0.7)	1997–1999	5.5 (2.7–9.0)	1575	44 (10.2)
12 (0.5)	172 (7.4)	8 (0.3)	1997–2001	11.5 (11.1–12.1)	22 006	40 (1.7)
26 (2.5)	17 (1.6)	2 (0.2)	1998	9.0 (8.3–9.2)	8453	14 (1.3)
91 (5.7)	NA	NA	1990–1993	15.5 (11.4–16.9)	20 892	226 (14.1)
384 (7.2)	57 (1.1)	11 (0.2)	1997–1999	3.3 (3.0–3.5)	16 529	496 (9.3)
607 (5.2)	NA	NA	1995–1998	17.0 (16.1–18.0)	137 861	575 (4.9)
37 (3.5)	20 (1.9)	1 (0.1)	1981	14.0 (14.0–14.0)	14 840	16 (1.5)
1958 (6.5)	733 (2.4)	35 (0.1)	1981–2008	16.6 (10.7–18.7)	278 955	2574 (8.6)
183 (10.4)	NA	NA	1978–1980	10.0 (NA)	NA	156 (8.9)
722 (8.3)	NA	NA	2000–2001 Cohort II, 2006–2008 Cohort III	6.8 (3.9–10.9)	61 935	403 (4.6)

AF indicates atrial fibrillation; EPIC, European Prospective Investigation of Cancer; Health ABC Study, Health, Aging, and Body Composition Study; InCHIANTI, Invecchiare in Chianti; IPD, individual participant data; IQR, interquartile range (25th–75th percentiles); MrOS, Osteoporotic Fractures in Men Study; NA, data not available; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; SHIP, Study of Health in Pomerania; and TSH, thyroid-stimulating hormone.

\*We excluded from our analyses participants with prevalent AF at baseline, missing outcomes for AF, subclinical hyperthyroidism and overt thyroid dysfunction, and intake of thyroxine or antithyroid medication at baseline.

†We excluded participants <18 years of age.

‡Cardiovascular disease at baseline was defined as a known history of stroke, transient ischemic attack, myocardial infarction, angina pectoris, coronary angioplasty, or bypass surgery.

§We used a common definition of subclinical hypothyroidism, TSH 4.5 mIU/L to 19.9 mIU/L and normal free thyroxine level, but TSH cutoff values varied among the previous reports from each cohort, so numbers are different than in the original articles. To analyze only endogenous subclinical hypothyroidism, we excluded 253 participants in the Cardiovascular Health Study, 207 in the Health ABC Study, 43 in the MrOS, 15 in the Bari study, 12 in the Leiden 85-plus study, 107 in the SHIP, 21 in CHIANTI, 26 in the Rotterdam study, 188 in the PROSPER study, 301 in the EPIC-Norfolk study, and 4 in the Busseton Health study because they used thyroid medication at baseline.

||We had no data on thyroid medication use during follow-up for 481 participants in the Study of Health in Pomerania, and all participants in the EPIC-Norfolk and the Rotterdam study. Ninety-one participants in the Cardiovascular Health Study did not have information on thyroxine during follow-up, and information on antithyroid medication during follow-up was missing for all patients of the Cardiovascular Health Study. Five persons took both thyroxine and antithyroid medication during the course of follow-up.

#For all cohorts, we used the maximal follow-up data that were available, which may differ from previous reports of some cohorts. For the Cardiovascular Health Study, we set the baseline for our analysis to the year 5 visit of the original cohort because free thyroxine was measured at the year 5 visit.

\*\*SHIP includes participants from Pomerania, where an iodine supplementation program began in the mid-1990s. This shifted the distribution of TSH values toward the left in its first years, which lowered TSH values in the population of the SHIP Study during baseline examinations in 1997 to 2001.

†† Number of participants with euthyroidism and subclinical hypothyroidism. Participants with subclinical hyperthyroidism are not listed here, because they were not included in our sensitivity analysis or in the aggregate data from this cohort.

‡‡ Data on characteristics of 8740 participants included in the longitudinal analysis by Chaker et al<sup>24</sup> was obtained through contact with the authors. Individual participant data of 1602 participants was available for Rotterdam Study Cohort I (see above).

elevated TSH 7.0 to 9.9 mIU/L, and markedly elevated TSH 10.0 to 19.9 mIU/L.<sup>10</sup> In some cohorts, we also included participants with missing ft4 measurements and a TSH within

the range for subclinical hypothyroidism in the main analyses (Table 2), because most people with TSH levels in this range have subclinical rather than overt thyroid dysfunction.<sup>7</sup> We

performed a sensitivity analysis, with exclusion of individuals with missing fT4 values.

Study-specific cutoffs were used for fT4 (Table 2) because intermethod variation is greater for these measurements than in TSH assays<sup>10</sup>; participants were categorized in fT4 quartiles.

We excluded those with overt thyroid dysfunction or thyroid hormone values that suggested nonthyroidal illness (low TSH and fT4 levels) or subclinical hyperthyroidism, because we have already published these results (this previous publication was based on a smaller number of studies, because new data became available after its publication in 2012).<sup>8</sup> To restrict our analysis to patients with endogenous values of thyroid function, participants on thyroid medication (thyroxine, antithyroid medication) at baseline were excluded (Figure 1 in the online-only Data Supplement), whereas those initiating thyroid medications during follow-up were included in the main analyses.<sup>8</sup> Additional sensitivity analyses excluding users of thyroid medication during follow-up were performed.

## Outcomes

The outcome was incident AF; participants with preexisting AF at baseline were excluded from all analyses. The ascertainment of AF included ECGs during follow-up (9 studies), self-report, diagnostic codes, and review of medical records depending on the cohorts (Table 2). Because AF ascertainment by self-report and review of medical records might be less specific, we performed a sensitivity analysis excluding studies with AF diagnosis without ECG review. Any type of AF (paroxysmal, persistent, permanent) was considered.

## Statistical Analyses

Differences in baseline characteristics of participants with euthyroidism and those with subclinical hypothyroidism were compared by using a  $\chi^2$  test or Student *t* test, as appropriate. Crude incidence rates for AF per 1000 person-years were calculated by using an inverse variance random-effects meta-analysis of log incidence rates, and point estimates and their 95% confidence intervals (CIs) were exponentiated to obtain the incidence rates. An IPD analysis was conducted by using a 1-step approach.<sup>18</sup> A Cox proportional hazard regression analysis using random effects (shared frailty) by cohort was used to describe the association between incident AF and TSH or fT4.<sup>38</sup> The proportional hazards assumption was met. For the analysis with TSH as the explanatory variable, euthyroid participants within the TSH category from 3.50 to 4.49 mIU/L were used as the reference group. The reference group was chosen according to the assumption of an S-shaped association between TSH and the risk of AF based on previous findings.<sup>11,14</sup> All TSH categories were analyzed in a single model. Following the recent publications of studies indicating an association between fT4 levels in the reference range and major adverse events including AF<sup>14,24</sup> and stroke,<sup>22</sup> we also conducted a secondary analysis (not prespecified in the study protocol) of the association between fT4 in the euthyroid range and AF; study-specific quartiles of fT4 were computed, and the lowest fT4 quartile was the reference group. Only participants with both TSH

and fT4 levels within the reference range were included in the secondary analysis.

The main analyses of both the association between TSH or fT4 and incidence of AF were adjusted for age and sex.<sup>10</sup> In a following step, additional adjustment was done for traditional cardiovascular risk factors, including systolic blood pressure, current or former smoking, diabetes mellitus, total cholesterol, and prevalent cardiovascular disease (multivariable adjusted analysis); because some of these risk factors might be mediators in the relationship between thyroid hormones and incidence of AF, the age- and sex-adjusted model was considered the main analysis. Whenever there was an indication of a linear association, we calculated *P* for linear trend for the main and multivariable adjusted analysis. Because data were not available in all cohorts, we also performed sensitivity analyses additionally adjusted for (1) antihypertensive and lipid-lowering medication and (2) body mass index. Additional sensitivity analyses (3) included all individuals regardless of intake of thyroid medication (thyroxine or antithyroid medication), so participants with thyroid medication use at baseline were added to this sensitivity analysis, (4) excluded participants who took amiodarone at baseline (or studies that did not provide this information), (5) excluded participants who took any other medications that might alter thyroid function (amiodarone, lithium, glucocorticoids, iodine, aspirin, and furosemide) at baseline, (6) excluded those having received thyroid medication during follow-up (or studies that did not provide this information), (7) excluded studies in which no ECGs were used to diagnose AF, (8) excluded studies with >5% lost to follow-up, and (9) excluded a study that tested thyroid function an average of 3.4 years before incident AF was first assessed.<sup>26</sup> For analyses of the association between TSH levels and the risk of AF, we also performed sensitivity analyses that (10) excluded participants whose fT4 measurements were missing; (11) were restricted to individuals with persistent thyroid function state, ie, included only those with thyroid function measurements that remained in the same category (euthyroidism or subclinical hypothyroidism) during follow-up thyroid function testing; and (12) excluded a study<sup>29</sup> conducted in a region where an iodine supplementation program was initiated a few years before the study was started, leading to a shift of TSH values toward lower levels in this population during the baseline examination.<sup>39</sup> All sensitivity analyses were prespecified in our protocol, with the exception of analyses 4, 9, 11, and 12.

To examine potential sources of heterogeneity, we conducted predefined subgroup analyses similar to those in our previous studies,<sup>8,10</sup> which considered age, sex, race, and the prevalence of cardiovascular disease. In an additional analysis, individuals with thyroxine use at baseline were included, and a subgroup analysis stratified on thyroxine use at baseline was performed. *P* values to test for interaction in the subgroup analyses were derived from Wald tests.

We analyzed the association between continuous concentrations of TSH or fT4 and AF. For the association between TSH and AF, a 4-knot restricted cubic spline was used with knots at TSH levels of 1.0 mIU/L, 2.5 mIU/L, 4.5 mIU/L, and 10 mIU/L, to represent 3 categories within the reference TSH range, and categories of subclinical hypothyroidism with mildly to moderately elevated TSH and markedly elevated TSH

**Table 2.** Definition of Subclinical Hypothyroidism and Atrial Fibrillation Events

Study	Cohort TSH and fT4 Reference Range	Definition of Subclinical Hypothyroidism in IPD Analysis	AF Events—Methods of Ascertainment
United States			
Cardiovascular Health Study	TSH 0.45–4.50 mIU/L, fT4 9–22 pmol/L	TSH $\geq$ 4.5 mIU/L & TSH <20 mIU/L, normal fT4 0.7–1.7 ng/dL (9–22 pmol/L) or missing fT4 (0/436, 0%)	Self-report, annual ECGs, ICD-9-coded AF on hospital discharge
Health ABC Study	TSH 0.1–4.4 mIU/L, fT4 10.3–23.2 pmol/L	TSH $\geq$ 4.5 mIU/L & TSH <20 mIU/L, normal fT4 0.8–1.8 ng/dL (10.3–23.2 pmol/L) or missing fT4 (195/270, 72%)*	Minnesota-coded ECGs at baseline and at year 4 follow-up, ICD-9-coded ambulatory and inpatient AF diagnoses from CMS data
MrOS Study	TSH 0.55–4.78 mIU/L, fT4 9–24 pmol/L	TSH $\geq$ 4.5 mIU/L & TSH <20 mIU/L, normal fT4 0.7–1.85 ng/dL (9–24 pmol/L) or missing fT4 (0/46, 0%)	ECG at baseline, self-report, AF diagnoses from medical records every 4 mo
Europe			
Bari Study	TSH 0.35–5.50 mIU/L, fT4 9–23.2 pmol/L	TSH $\geq$ 4.5 mIU/L & TSH <20 mIU/L, normal fT4 0.7–1.8 ng/dL (9–23.2 pmol/L) or missing fT4 (0/23, 0%)	ICD-9-coded AF on hospital discharge
Leiden 85-plus Study	TSH 0.3–4.8 mIU/L, fT4 13–23 pmol/L	TSH $\geq$ 4.5 mIU/L & TSH <20 mIU/L, normal fT4 1.0–1.8 ng/dL (13–23 pmol/L) or missing fT4 (1/27, 3.7%)	Minnesota-coded annual ECGs
Study of Health in Pomerania	TSH 0.25–2.12 mIU/L, fT4 8.3–18.9 pmol/L	TSH $\geq$ 4.5 mIU/L & TSH <20 mIU/L, normal fT4 0.64–1.47 ng/dL (8.3–18.9 pmol/L) or missing fT4 (0/12, 0%)	Minnesota-coded ECGs at baseline, year 5, and year 10 follow-up
Invecchiare in Chianti Study	TSH 0.46–4.68 mIU/L, fT4 9.9–28.2 pmol/L	TSH $\geq$ 4.5 mIU/L & TSH <20 mIU/L, normal fT4 0.77–2.19 ng/dL (9.9–28.2 pmol/L) or missing fT4 (0/26, 0%)	ECGs at baseline, 3-y, 6-y, and 9-y follow-up
Rotterdam Study	TSH 0.4–4.0 mIU/L, fT4 11–25 pmol/L	TSH $\geq$ 4.5 mIU/L & TSH <20 mIU/L, normal fT4 0.9–1.9 ng/dL (11–25 pmol/L) or missing fT4 (29/91, 31.9%)	ECGs at baseline, year 2 and year 7 follow-up, ICD-10-coded AF diagnoses from GP records and hospital discharge
PROSPER Study	TSH 0.45–4.50 mIU/L, fT4 12–18 pmol/L	TSH $\geq$ 4.5 mIU/L & TSH <20 mIU/L, normal fT4 0.9–1.4 ng/dL (12–18 pmol/L) or missing fT4 (211/384, 54.9%)†	Minnesota-coded annual ECGs
EPIC-Norfolk Study	TSH 0.4–4.0 mIU/L, fT4 9–20 pmol/L	TSH $\geq$ 4.5 mIU/L & TSH <20 mIU/L, normal fT4 0.7–1.6 ng/dL (9–20 pmol/L) or missing fT4 (0/607, 0%)	Self-reported intake of drugs used for AF treatment at baseline (digitalis and VKAs), ICD-10-coded AF on hospital discharge
Australia			
Busselton Health Study	TSH 0.4–4.0 mIU/L, fT4 9–23 pmol/L	TSH $\geq$ 4.5 mIU/L & TSH <20 mIU/L, normal fT4 0.7–1.8 ng/dL (9–23 pmol/L) or missing fT4 (1/37, 2.7%)	Minnesota-coded ECGs at baseline and at year 14 follow-up

AF indicates atrial fibrillation; EPIC, European Prospective Investigation of Cancer; fT4, free thyroxine; GP, general practitioner; Health ABC, Health, Aging, and Body Composition; ICD-9, *International Classification of Diseases, Ninth Revision*; ICD-10, *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; IPD, individual participant data; MrOS, Osteoporotic Fractures in Men Study; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; TSH, thyroid-stimulating hormone; and VKA, vitamin K antagonist.

\*fT4 was measured only in participants with TSH  $\geq$  7.0 mIU/L or TSH in this cohort.

†fT4 was measured only in participants with TSH  $\geq$ 4.5 mIU/L in this cohort.

levels, as well.<sup>10</sup> Hazard ratios (HRs) were compared with a reference value of 3.5 mIU/L, according to the lower bound of the cutoff used for our reference category. For the association between continuous concentrations of fT4 within the reference range and AF, we expressed fT4 in SD units centered around the mean to make fT4 values comparable across studies. For this analysis, we used a 1-knot restricted cubic spline with the knot placed at the median value of fT4 in SD units, which resulted in the best model fit. Spline regression analyses were adjusted for age and sex. We calculated a *P* for nonlinear trend using a likelihood ratio test comparing the models with and without the TSH or fT4 splines, respectively. This analysis was not prespecified in our protocol. Statistical significance was tested 2-sided, and *P* values of <0.05 were judged significant. We used inverse variance random-effects meta-analysis to combine the summary estimates of our IPD analysis with results from 2 studies that provided only aggregate data. We used a funnel plot to assess for potential

publication bias of the association between fT4 levels within the reference range and the risk of AF, considering the estimates of the highest quartile of fT4 in comparison with the lowest quartile. All analyses were conducted by using Stata version 14.1 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.).

## RESULTS

Of the 1418 identified reports, 14 prospective studies met our eligibility criteria (Figure II in the online-only Data Supplement and Table II in the online-only Data Supplement). Among those, 6 studies<sup>9,13,14,16,24,31</sup> were published, and 8 cohorts<sup>25–30,32,33</sup> offered previously unpublished data. Because 2 of the studies included the same population, we contacted 13 cohorts and asked them to share IPD. Of these, 11 international cohorts

(from Europe, the United States, and Australia) agreed to provide IPD, and we added summary estimates of 2 studies that did not provide IPD in random-effects models as sensitivity analyses.

After exclusion of participants with thyroxine and antithyroid medication use at baseline, 30 085 individuals were included in the final analysis (Figure I in the online-only Data Supplement). Among included participants, the median age was 69 years at inclusion, 51.6% were women, 28 127 individuals were euthyroid, and 1958 (6.5%) had endogenous subclinical hypothyroidism. Median follow-up ranged from 1.3 to 17 years across the different studies, adding up to 278 955 person-years of follow-up; during this time, 2574 individuals (8.6%) developed incident AF. Thyroid medication use (thyroxine and antithyroid medication) during follow-up varied from 1.2% to 11.2% in the various studies (Table 1). In comparison with participants with euthyroidism, those with subclinical hypothyroidism were older, more likely to be women, or more likely to be affected by affected by comorbidities including cardiovascular disease or diabetes mellitus (Table III in the online-only Data Supplement).

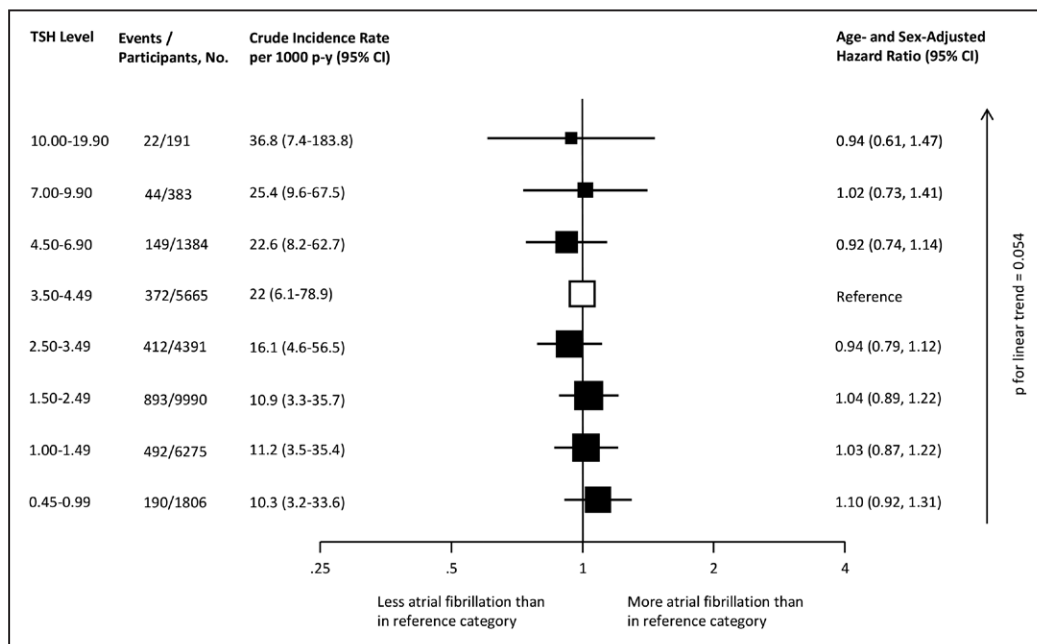
Overall study quality was high; all included studies scored  $\geq 6$  points on the Newcastle-Ottawa Quality Assessment Scale. All cohorts were community based, and 2 cohorts<sup>27,32</sup> did not use ECG review to diagnose AF. Length of follow-up was  $>5$  years, except for 2 studies,<sup>27,31</sup> and loss of follow-up was  $<5\%$  in 6 studies (Table IV in the online-only Data Supplement).

## TSH Within the Reference Range and the Risk of AF

Crude incidence rates are presented in Figure 1. In age- and sex-adjusted analyses, there was no association between TSH levels in the reference range and risk of AF (Figure 1). When analyzing continuous concentrations of TSH, the risk of AF increased with low-normal TSH levels and slightly decreased with higher TSH levels (but remained close to a HR of 1.0) in comparison with the reference level of 3.5 mIU/L (Figure III in the online-only Data Supplement). Sensitivity analyses yielded similar results (Table 3 and Table V in the online-only Data Supplement), and no significant interaction was found when analyses were stratified according to sex, age, or previous cardiovascular disease. In the analysis with additional inclusion of individuals with thyroxine use at baseline, point estimates were higher among thyroxine users than among those not on thyroxine in a subgroup analysis, but without statistical significance likely because of the limited number of thyroxine users (n=1146, Table VI in the online-only Data Supplement).

## Subclinical Hypothyroidism and the Risk of AF

In comparison with the reference level of 3.50 to 4.49 mIU/L, subclinical hypothyroidism was not associated with incident AF in age- and sex-adjusted analyses, with a HR of 0.92 (95% CI, 0.74–1.14) for a TSH level of 4.5 to 6.9 mIU/L, a HR of 1.02 (95% CI, 0.73–1.41) for a TSH level of 7.0 to 9.9 mIU/L, and a HR of 0.94



**Figure 1. Association between thyroid-stimulating hormone and the risk of atrial fibrillation.**

Participants who used thyroid hormones at baseline were excluded. CI indicates confidence interval; p-y, person-years; and TSH, thyroid-stimulating hormone.

**Table 3. Main and Sensitivity Analysis of the Association Between Thyroid-Stimulating Hormone Within the Reference Range and the Risk of Atrial Fibrillation**

	TSH Level (mIU/L)									
	0.45–0.99		1.00–1.49		1.50–2.49		2.50–3.49		3.50–4.49	
	Events/ Persons	HR (95% CI)	Events/ Persons	HR (95% CI)	Events/ Persons	HR (95% CI)	Events/ Persons	HR (95% CI)	Events/ Persons	HR (95% CI)
All available cohorts										
Age- and sex-adjusted	372/5665	1.10 (0.92–1.31)	492/6275	1.03 (0.87–1.22)	893/9990	1.04 (0.89–1.22)	412/4391	0.94 (0.79–1.12)	190/1806	ref.
Multivariable adjusted analysis*	370/5611	1.07 (0.89–1.28)	487/6199	0.99 (0.84–1.18)	882/9841	1.02 (0.87–1.19)	410/4336	0.92 (0.78–1.10)	187/1777	ref.
Further adjustments of multivariable models*										
Plus antihypertensive and lipid-lowering medication	357/4924	1.06 (0.88–1.27)	469/5699	0.98 (0.83–1.17)	862/9297	1.01 (0.86–1.19)	405/4138	0.94 (0.78–1.12)	180/1703	ref.
Plus BMI	356/4911	1.07 (0.89–1.29)	466/5682	0.99 (0.84–1.18)	855/9257	1.02 (0.87–1.20)	403/4120	0.94 (0.79–1.13)	179/1696	ref.
Medication affecting thyroid function										
Including all regardless of thyroid medication use†	399/5920	1.10 (0.92–1.31)	516/6437	1.05 (0.89–1.24)	925/10226	1.06 (0.91–1.23)	432/4533	0.96 (0.81–1.14)	200/1914	ref.
Excluding thyroid medication use at BL and/or FUP‡	370/5552	1.10 (0.91–1.32)	483/6217	1.01 (0.85–1.21)	881/9902	1.04 (0.88–1.22)	393/4305	0.93 (0.78–1.11)	173/1722	ref.
Excluding users of amiodarone§	367/5639	1.09 (0.91–1.30)	490/6254	1.03 (0.87–1.21)	889/9958	1.04 (0.89–1.22)	408/4380	0.94 (0.78–1.11)	190/1795	ref.
Excluding users of other drugs affecting thyroid function¶	241/4536	1.21 (0.96–1.53)	302/4815	1.12 (0.89–1.40)	531/7364	1.13 (0.91–1.40)	222/3059	0.99 (0.78–1.25)	103/1273	ref.
Thyroid function										
Excluding participants with missing values of ft4#	288/4808	1.10 (0.89–1.34)	365/4983	1.01 (0.83–1.22)	650/7561	1.01 (0.85–1.21)	289/3097	0.90 (0.74–1.10)	147/1314	ref.
Including only participants with persistent thyroid function state**	62/905	0.96 (0.61–1.51)	102/1304	1.04 (0.68–1.60)	214/2237	1.20 (0.81–1.80)	78/985	0.91 (0.59–1.41)	27/314	ref.
Excluding studies										
Excluding studies with AF diagnosis without ECG review††	282/3912	1.13 (0.92–1.39)	356/3651	1.05 (0.86–1.27)	683/5517	1.11 (0.93–1.33)	334/2673	1.00 (0.82–1.21)	147/1094	ref.
Excluding studies with >5% lost to follow-up‡‡	236/3100	1.05 (0.83–1.33)	324/4515	1.00 (0.80–1.25)	574/7851	1.03 (0.83–1.28)	233/3407	0.89 (0.71–1.13)	99/1354	ref.
Excluding MrOS Study§§	364/5595	1.10 (0.92–1.32)	477/6144	1.03 (0.87–1.23)	874/9752	1.06 (0.90–1.25)	402/4254	0.96 (0.81–1.14)	182/1749	ref.
Excluding SHIP Study¶¶	343/4046	1.10 (0.92–1.32)	483/5775	1.02 (0.86–1.21)	891/9820	1.04 (0.89–1.22)	412/4359	0.94 (0.79–1.12)	190/1800	ref.

AF indicates atrial fibrillation; BMI, body mass index; BL, baseline; CI, confidence interval; EPIC, European Prospective Investigation of Cancer; ft4, free thyroxine; FUP, follow-up; Health ABC, Health, Aging, and Body Composition; HR, hazard ratio; MrOS, Osteoporotic Fractures in Men Study; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; ref., reference; SHIP, Study of Health in Pomerania; and TSH, thyroid-stimulating hormone.

\*Adjusted for age, sex, systolic blood pressure, current and former smoking, diabetes mellitus, total cholesterol, and prevalent cardiovascular disease at baseline.

†For this sensitivity analysis, we added a total of 1177 thyroid medication users (thyroxine or antithyroid drugs) to the overall sample: 253 participants in the Cardiovascular Health Study; 207 in the Health ABC Study; 43 in the MrOS; 15 in the Bari Study; 12 in the Leiden 85-plus Study; 107 in the SHIP; 21 in the Invecchiare in Chianti Study; 26 in the Rotterdam Study; 188 in the PROSPER Study; 301 in the EPIC-Norfolk Study; and, 4 in the Busseton Health Study.

‡The number of thyroid medication users (thyroxine or antithyroid drugs) during follow-up is indicated in Table 1.

§A total of 123 participants who took amiodarone were excluded for this sensitivity analysis of the association between TSH and AF: 2 participants in the Cardiovascular Health Study; 3 in the Health ABC Study; 1 in the MrOS; 79 in the Bari Study; 1 in the Leiden 85-plus Study; 1 in the SHIP; 6 in the Invecchiare in Chianti Study; 6 in the Rotterdam Study; 23 in the PROSPER Study; and 1 in the EPIC-Norfolk Study. Information on amiodarone use was not available in the Busseton Health Study.

¶A total of 7786 participants who took other medications that could alter thyroid levels (corticosteroids, amiodarone, iodine, lithium, aspirin, furosemide) were excluded for this sensitivity analysis: 1634 participants in the Cardiovascular Health Study; 881 in the Health ABC Study; 245 in the MrOS; 251 in the Bari Study; 56 in the Leiden 85-plus Study; 299 in the SHIP; 122 in the Invecchiare in Chianti Study; 151 in the Rotterdam Study; 3199 in the PROSPER Study; 948 in the EPIC-Norfolk Study.

#A total of 311 participants were excluded for this analysis: 22 participants in the Cardiovascular Health Study; 5 in the Leiden 85-plus Study; 1 in the Invecchiare in Chianti Study; 282 in the Rotterdam Study; and 1 in the Busseton Health Study had missing measurements for ft4. In participants in the Health ABC study, ft4 was measured only in participants with TSH  $\geq$ 7.0 mIU/L (therefore, no ft4 measurement in 2270 participants), and, in the PROSPER Study, ft4 was measured only in participants with TSH <0.45 mIU/L or TSH  $\geq$ 4.5 mIU/L (therefore, no ft4 measurement in 4220 participants).

\*\*Persistent thyroid function state was defined as persistent category (euthyroidism, subclinical hypothyroidism) from baseline to follow-up thyroid function test. Follow-up thyroid function was measured in the Cardiovascular Health Study, Leiden 85-plus Study, PROSPER Study, SHIP, and the Busseton Health Study.

††The Bari and EPIC-Norfolk studies were excluded.

‡‡The Cardiovascular Health Study, MrOS Study, SHIP Study, Invecchiare in Chianti Study, and Busseton Health Study were excluded.

§§In the MrOS Study, thyroid hormones were measured an average of 3.4 years before other baseline characteristics were assessed.

¶¶SHIP includes participants from Pomerania, where an iodine supplementation began in the mid-1990s, which shifted the distribution of TSH values toward the left during the first years, and lowered TSH values in the population in the SHIP Study during the baseline examinations in 1997 to 2001.

**Table 4. Main and Sensitivity Analysis of the Association Between Subclinical Hypothyroidism and the Risk of Atrial Fibrillation**

	TSH Level (mIU/L)							
	3.50–4.49		4.5–6.9		7.0–9.9		10.0–19.9	
	Events/ Participants	HR (95% CI)	Events/ Participants	HR (95% CI)	Events/ Participants	HR (95% CI)	Events/ Participants	HR (95% CI)
All available cohorts								
Age- and sex-adjusted	190/1806	ref.	149/1384	0.92 (0.74–1.14)	44/383	1.02 (0.73–1.41)	22/191	0.94 (0.61–1.47)
Multivariable adjusted analysis*	187/1777	ref.	149/1365	0.91 (0.74–1.14)	43/377	0.95 (0.68–1.33)	22/189	0.93 (0.60–1.44)
Further adjustments of multivariable models*								
Plus antihypertensive and lipid-lowering medication	180/1703	ref.	146/1316	0.92 (0.74–1.14)	41/363	0.92 (0.66–1.30)	22/176	0.95 (0.61–1.48)
Plus BMI	179/1696	ref.	144/1307	0.92 (0.74–1.15)	41/362	0.93 (0.66–1.31)	22/176	0.96 (0.61–1.49)
Medication affecting thyroid function								
Including all regardless of thyroid medication use†	200/1914	ref.	162/1521	0.91 (0.74–1.12)	47/457	0.92 (0.67–1.26)	33/254	1.09 (0.75–1.57)
Excluding thyroid medication use at BL and/or FUP‡	173/1722	ref.	111/1208	0.89 (0.70–1.13)	35/296	1.27 (0.88–1.83)	12/120	1.07 (0.60–1.93)
Excluding users of amiodarone	190/1795	ref.	148/1376	0.92 (0.74–1.14)	44/377	1.02 (0.74–1.42)	20/183	0.89 (0.56–1.42)
Excluding users of other drugs affecting thyroid function§	103/1273	ref.	81/891	1.08 (0.81–1.44)	27/243	1.29 (0.84–1.97)	11/118	1.15 (0.62–2.14)
Thyroid function								
Excluding participants with missing values of fT4	147/1314	ref.	124/997	0.98 (0.77–1.24)	40/339	1.02 (0.71–1.45)	22/185	0.98 (0.62–1.54)
Including only participants with persistent thyroid function state#	27/314	ref.	10/159	0.70 (0.34–1.44)	4/84	0.55 (0.19–1.57)	6/43	1.70 (0.70–4.12)
Excluding studies								
Excluding studies with AF diagnosis without ECG review**	147/1094	ref.	131/951	0.99 (0.78–1.25)	33/245	0.95 (0.65–1.39)	19/132	1.02 (0.63–1.65)
Excluding studies with >5% lost to follow-up††	99/1354	ref.	60/992	0.78 (0.56–1.07)	22/280	1.10 (0.69–1.74)	8/130	0.76 (0.37–1.57)
Excluding MrOS Study‡‡	182/1749	ref.	148/1351	0.95 (0.76–1.18)	43/374	1.03 (0.74–1.43)	22/188	0.96 (0.62–1.50)
Excluding SHIP Study§§	190/1800	ref.	149/1374	0.92 (0.74–1.14)	44/382	1.02 (0.73–1.41)	22/190	0.94 (0.61–1.47)

AF indicates atrial fibrillation; BMI, body mass index; BL, baseline; CI, confidence interval; EPIC, European Prospective Investigation of Cancer; fT4, free thyroxine; FUP, follow-up; Health ABC, Health, Aging, and Body Composition; HR, hazard ratio; MrOS, Osteoporotic Fractures in Men Study; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; ref., reference; SHIP, Study of Health in Pomerania; and TSH, thyroid-stimulating hormone.

\*Adjusted for age, sex, systolic blood pressure, current and former smoking, diabetes mellitus, total cholesterol, and prevalent cardiovascular disease at baseline.

†Thyroid medication was defined as thyroxine or antithyroid drugs.

‡The numbers of thyroid medication users during follow-up are indicated in Table 1.

§Other medications that could alter thyroid levels: corticosteroids, amiodarone, iodine, lithium, aspirin, and furosemide.

||A total of 311 participants were excluded for this analysis: fT4 measurements were missing for 22 participants in the Cardiovascular Health Study, 5 in the Leiden 85-plus Study, 1 in the Invecchiare in Chianti Study, 282 in the Rotterdam Study, and 1 in the Busselton Health Study. In participants of the Health ABC study, fT4 was measured only in those with TSH  $\geq 7.0$  mIU/L (therefore, no fT4 measurement in 2270 participants); in the PROSPER Study, fT4 was measured only in participants with TSH  $< 0.45$  mIU/L or TSH  $\geq 4.5$  mIU/L (therefore, no fT4 measurement in 4220 participants).

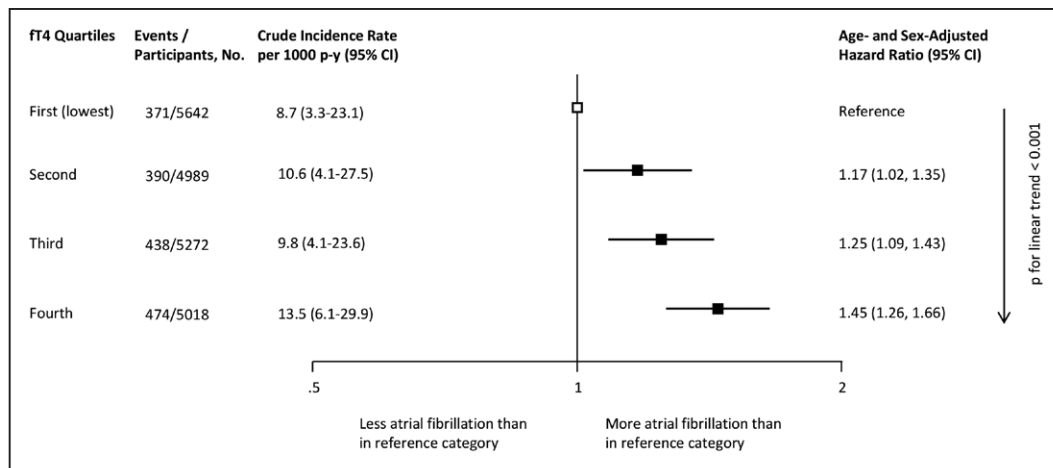
#Persistent thyroid function state was defined as persistent category (euthyroidism, subclinical hypothyroidism) from baseline to follow-up thyroid function test. Follow-up thyroid function was measured in the Cardiovascular Health Study, Leiden 85-plus Study, PROSPER Study, the SHIP, and the Busselton Health Study.

\*\*The Bari and EPIC-Norfolk studies were excluded.

††The Cardiovascular Health Study, MrOS, SHIP, Invecchiare in Chianti Study, and Busselton Health Study were excluded.

‡‡In the MrOS, thyroid hormones were measured an average of 3.4 years before AF was first assessed.

§§SHIP includes participants from Pomerania, where an iodine supplementation began in the mid-1990s, which shifted the distribution of TSH values toward the left during the first years, and lowered TSH values in the population in the SHIP Study during the baseline examinations in 1997 to 2001.



**Figure 2. Association between quartiles of free thyroxine within the reference range and the risk of atrial fibrillation.** The reference range for TSH was defined as 0.45 to 4.49 mIU/L. For ft4, we used study-specific cutoff values. Participants who used thyroid hormones at baseline were excluded. CI indicates confidence interval; ft4, free thyroxine; and p-y, person-years.

(95% CI, 0.61–1.47) for a TSH level of 10.0 to 19.9 mIU/L (Table 4). The results remained similar in sensitivity analyses (Table 4 and Table VII in the online-only Data Supplement), and analyses stratified by sex, age, previous cardiovascular disease, and thyroxine use at baseline showed no significant interaction (Table VIII in the online-only Data Supplement). Adding overall relative risks (HRs not reported) of 1 study from which we were not able to obtain IPD<sup>9</sup> yielded similar results for the association between subclinical hypothyroidism and AF (HR, 1.07; 95% CI, 0.72–1.58).

### ft4 Within the Reference Range and the Risk of AF

Crude incidence rates are shown in Figure 2. Among the 30085 individuals included in our study, 20921 were included in the analysis of the association between ft4 and AF, having both their TSH and ft4 within the reference range. In those individuals, higher ft4 levels at baseline were associated with increased risk of AF in age- and sex-adjusted analyses, with a HR of 1.17 (95% CI, 1.02–1.35) in the second quartile, a HR of 1.25 (95% CI, 1.09–1.43) in the third, and a HR of 1.45 (95% CI, 1.26–1.66) in the fourth quartile in comparison with the first (lowest) quartile of ft4 levels ( $P$  for trend across ft4 levels  $\leq 0.001$ ) (Figure 2). When modeled as a continuous variable, increasing ft4 levels within the reference range were associated with an increased risk of AF (Figure IV in the online-only Data Supplement). In analyses with multivariable adjustment for age, sex, systolic blood pressure, smoking, diabetes mellitus, total cholesterol, and prevalent cardiovascular disease at baseline, HRs remained similar. Further adjustments for antihypertensive medication, lipid-lowering medication, and body mass index

did not significantly change the results. Sensitivity analyses yielded similar results (Table 5 and Table IX in the online-only Data Supplement). Risks were similar when all individuals regardless of thyroid medication use at baseline were included, or after excluding studies without AF diagnosis by ECG review,<sup>27,32</sup> or when excluding a study<sup>26</sup> that started follow-up of incident AF an average of 3.4 years after baseline thyroid function was measured. Estimates did not change substantially after we added the aggregate results from a study that did not provide IPD.<sup>24</sup>

Stratified results are presented in Figure 3 and Table X in the online-only Data Supplement. In comparison with those without known cardiovascular disease, participants with previous cardiovascular disease showed no association between ft4 levels and AF risk. However, this finding might be affected by selection bias attributable to the exclusion of participants with prevalent AF at baseline. Risks did not differ substantially according to age, sex, and race. In an additional analysis including thyroxine users, risks were similar irrespective of thyroxine intake at baseline.

### Assessment of Potential Publication Bias

Visual inspection of the funnel plot did not suggest publication bias for the association between ft4 within the reference range and the risk of AF (Figure V in the online-only Data Supplement).

## DISCUSSION

Our IPD analysis including 30085 individuals from 11 prospective cohorts showed no association between TSH levels within the reference range or subclinical hypothyroidism and risk of AF. In euthyroid individuals,

**Table 5. Main and Sensitivity Analysis of the Association Between Quartiles of Free Thyroxine Within the Reference Range and the Risk of Atrial Fibrillation\***

	fT4 Quartile								
	First Quartile		Second Quartile		Third Quartile		Fourth Quartile		P for trend
	Events/Participants	HR (95% CI)	Events/Participants	HR (95% CI)	Events/Participants	HR (95% CI)	Events/Participants	HR (95% CI)	
All available cohorts									
Age- and sex-adjusted	371/5642	ref.	390/4989	1.17 (1.02–1.35)	438/5272	1.25 (1.09–1.43)	474/5018	1.45 (1.26–1.66)	≤0.001
Multivariable adjusted analysis†	367/5551	ref.	384/4912	1.16 (1.00–1.33)	429/5198	1.19 (1.04–1.37)	472/4947	1.39 (1.22–1.60)	≤0.001
Further adjustments of multivariable model†									
Plus antihypertensive and lipid-lowering medication	358/4949	ref.	368/4526	1.12 (0.97–1.30)	415/4693	1.15 (1.00–1.32)	450/4494	1.31 (1.14–1.50)	≤0.001
Plus BMI	354/4928	ref.	366/4507	1.13 (0.98–1.31)	410/4669	1.15 (1.00–1.33)	447/4469	1.33 (1.16–1.53)	≤0.001
Medication affecting thyroid function									
Including all regardless of thyroid medication use‡	380/5731	ref.	429/5194	1.18 (1.03–1.36)	447/5466	1.29 (1.12–1.48)	487/5089	1.43 (1.25–1.63)	≤0.001
Excluding thyroid medication use at BL and/or FUP§	355/5533	ref.	390/4969	1.15 (1.00–1.33)	407/5105	1.25 (1.08–1.44)	467/4966	1.46 (1.27–1.67)	≤0.001
Excluding users of amiodarone¶	369/5626	ref.	391/4969	1.18 (1.03–1.36)	437/5265	1.25 (1.09–1.44)	468/4998	1.44 (1.25–1.65)	≤0.001
Excluding users of other drugs affecting thyroid function#	236/4676	ref.	250/4183	1.13 (0.95–1.36)	288/4359	1.30 (1.10–1.55)	301/4114	1.44 (1.21–1.70)	≤0.001
Excluding studies									
Excluding studies with AF diagnosis without ECG review**	257/2710	ref.	282/2331	1.24 (1.05–1.47)	293/2545	1.21 (1.02–1.43)	300/2354	1.39 (1.18–1.64)	≤0.001
Excluding studies with >5% lost to follow-up††	174/3517	ref.	181/3202	1.12 (0.91–1.37)	211/3306	1.27 (1.04–1.55)	237/3202	1.44 (1.18–1.75)	≤0.001
Excluding MrOS Study‡‡	361/5475	ref.	373/4837	1.15 (1.00–1.33)	424/5126	1.24 (1.07–1.42)	457/4864	1.43 (1.24–1.64)	≤0.001
Aggregate data									
Including aggregate data of the Rotterdam Study Cohorts I, II, and III§§	402/7186	ref.	428/6545	1.15 (1.01–1.32)	473/6812	1.22 (1.07–1.39)	533/6545	1.45 (1.27–1.65)	0.017

AF indicates atrial fibrillation; BMI, body mass index; BL, baseline; CHS, Cardiovascular Health Study; CI, confidence interval; EPIC, European Prospective Investigation of Cancer; fT4, free thyroxine; FUP, follow-up; Health ABC, Health, Aging, and Body Composition; HR, hazard ratio; MrOS, Osteoporotic Fractures in Men Study; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; ref., reference; SHIP, Study of Health in Pomerania; and TSH, thyroid-stimulating hormone.

\*This analysis was restricted to normal thyroid function (TSH and fT4 in the reference range). From the overall sample, we excluded 9164 participants for this analysis because their fT4 measurements were missing or their thyroid function was outside the reference range: 479 participants in the CHS; 59 in the MrOS; 32 in the Bari Study; 137 in the Leiden 85-plus Study; 125 in the SHIP; 42 in the Invecchiare in Chianti Study; 365 in the Rotterdam Study; 897 in the EPIC-Norfolk Study; and, 57 in the Busseton Health Study. In participants of the Health ABC Study, fT4 was measured only in TSH ≥ 7.0 mIU/L, so we excluded all 2346 participants for this analysis. In the PROSPER Study, fT4 was measured only in participants with TSH <0.45 mIU/L or TSH ≥4.5 mIU/L, so, 4625 participants were excluded from this analysis. The first quartile was the lowest one.

†Adjusted for age, sex, systolic blood pressure, current and former smoking, diabetes mellitus, total cholesterol, and prevalent cardiovascular disease at baseline.

‡A total of 559 participants with thyroid medication use (thyroxin or antithyroid drugs) at baseline were additionally added for this analysis: 167 participants in the CHS; 33 in the MrOS; 9 in the Bari Study; 5 in the Leiden 85-plus Study; 85 in the SHIP; 16 in the Invecchiare in Chianti Study; 9 in the Rotterdam Study; 8 in the PROSPER Study; 224 in the EPIC-Norfolk Study; and 3 in the Busseton Health Study.

§A total of 348 participants were on thyroid medication during follow-up: 139 participants in the CHS; 11 in the MrOS; 15 in the Bari Study; 3 in the Leiden 85-plus Study; 156 in the SHIP; 13 in the Invecchiare in Chianti Study; 2 in the PROSPER Study; and 9 in the Busseton Health Study.

¶A total of 63 participants who took amiodarone were excluded for this sensitivity analysis of the association between fT4 and AF: 1 participant in the CHS; 1 in the MrOS; 57 in the Bari Study; 3 in the Invecchiare in Chianti Study; and 1 in the EPIC-Norfolk Study. Information on amiodarone use was not available in the Busseton Health Study.

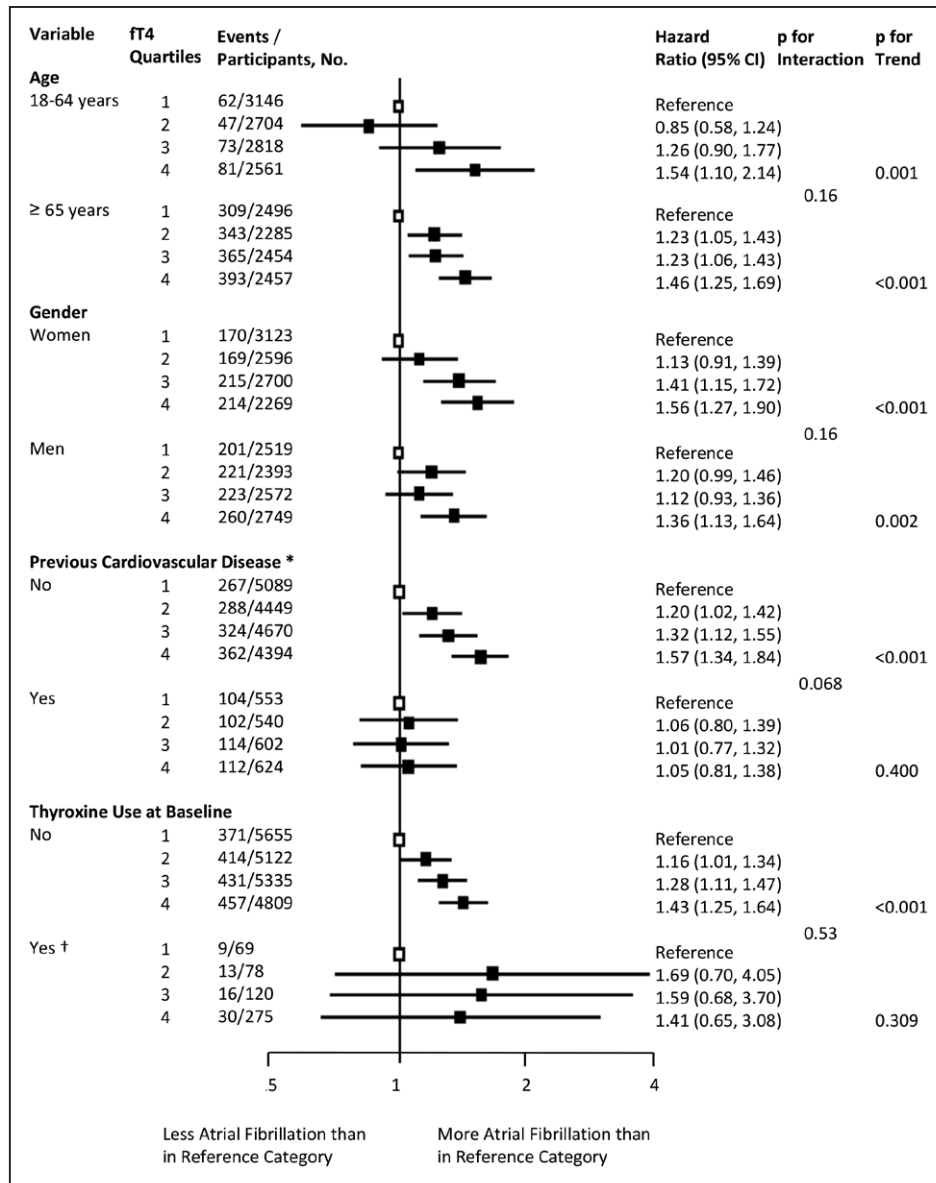
#We excluded a total of 3589 participants with intake of other medications that could alter thyroid levels (corticosteroids, amiodarone, iodine, lithium, aspirin, and furosemide) for this analysis: 1395 participants in the CHS; 215 in the MrOS Study; 220 in the Bari Study; 33 in the Leiden 85-plus Study; 286 in the SHIP; 111 in the Invecchiare in Chianti Study; 103 in the Rotterdam Study; 348 in the PROSPER Study; and 878 in the EPIC-Norfolk Study.

\*\*The Bari and EPIC-Norfolk studies were excluded. We excluded a total of 10981 participants from this sensitivity analysis: 236 participants in the Bari Study, and 10745 in the EPIC-Norfolk Study.

††The CHS, MrOS Study, SHIP Study, Invecchiare in Chianti Study, and Busseton Health Study were excluded.

‡‡In the MrOS Study, thyroid hormones were measured an average of 3.4 years before the first assessment of AF.

§§Individual participant data were not available from the study by Chaker et al,<sup>24</sup> which included aggregate results from the Rotterdam Study Cohorts I, II, and III. For this sensitivity analysis, we excluded individual participant data from the Rotterdam Study Cohort I (1244 participants with 171 events) that we had obtained from an earlier publication<sup>16</sup> to avoid duplicate participants.



**Figure 3. Stratified analyses for the association between quartiles of free thyroxine within the reference range and the risk of atrial fibrillation.**

We defined the reference range for TSH as 0.45 to 4.49 mIU/L and used study-specific cutoff values for fT4; the first fT4 quartile was the lowest one. The *P* for trend refers to a linear trend. CI indicates confidence interval; fT4, free thyroxine; and TSH, thyroid-stimulating hormone. \*Previous cardiovascular disease was defined as a history of stroke, transient ischemic attack, myocardial infarction, angina pectoris, coronary angioplasty, or bypass surgery. †542 participants with available fT4 measurements and normal thyroid function were on thyroxine at baseline: 167 participants in the CHS (Cardiovascular Health Study); 33 in the MrOS (Osteoporotic Fractures in Men Study); 6 in the Bari Study; 5 in the Leiden 85-plus Study; 76 in SHIP (Study of Health in Pomerania); 11 in the InCHIANTI Study (Invecchiare in Chianti); 9 in the Rotterdam Study; 8 in the PROSPER Study (Prospective Study of Pravastatin in the Elderly at Risk); 224 in the EPIC (European Prospective Investigation of Cancer)-Norfolk Study; and 3 in the Busselton Health Study.

we found a significant increase in the risk of AF with increasing fT4 levels within the reference range. Risks did not differ significantly by age and sex.

To our knowledge, our study is the first IPD analysis of prospective cohorts on the association between thyroid function in the reference range or subclinical hypothyroidism and the risk of AF. Our study was

strengthened by its large sample size, which allowed us to assess risks in subgroups by TSH levels in the normal range. Furthermore, our results were robust across all sensitivity analyses. By conducting an IPD analysis, our results are free of potential aggregation bias found in study-level meta-analyses,<sup>18</sup> and we could explore the impact of age, sex, and thyroid medication in subgroup

analyses. This approach also enabled us to standardize definitions of predictors and outcomes, use uniform adjustments for potential confounders to reduce heterogeneity across studies, and include unpublished data to increase the robustness of our results and power to detect associations. IPD analyses are the ideal approach to aggregating evidence by pooling estimates from multiple studies.<sup>19</sup>

Our study confirmed previous results from 2 recent prospective population-based studies that found an increased risk of AF in higher fT4 levels in euthyroid individuals, whereas TSH levels were not associated with AF.<sup>14,24</sup> Similar results were shown in a cross-sectional study that included older adults.<sup>17</sup> Recently, a large Danish retrospective register study of more than half a million individuals found a linear increase in risk of incident AF with decreasing TSH levels, resulting in a protective effect of subclinical hypothyroidism on AF in comparison with the euthyroid state. Participants in the high-normal euthyroidism subgroup defined as TSH of 0.2 to 0.4 mIU/L with thyroxine levels in the reference range had a higher AF risk (incident rate ratio, 1.12; 95% CI, 1.03–1.21) than low-normal euthyroidism, defined as TSH 0.4 to 5.0 mIU/L.<sup>11</sup> However, the investigators chose different TSH cutoff values than used in our and other studies,<sup>8,9,13,16,17</sup> and defined the TSH range 0.2 to 0.4 mIU/L as high-normal euthyroidism (which was defined as subclinical hyperthyroidism in our study); strictly speaking, risk of AF within the euthyroid range with a TSH of 0.4 to 5.0 mIU/L has not been investigated. In contrast to the Danish study, we identified no significant association between subclinical hypothyroidism with AF, but our results showed a similar trend across higher TSH levels. However, the Danish study was based on retrospective administrative data, which have inherent drawbacks, including potential confounding by indication (TSH was not randomly ordered by general practitioners) and no ECG confirmation of AF. In contrast, the results of the Framingham Heart Study aligned with ours: no association between TSH levels above the reference range and the risk of AF was found among 5069 participants during a 10-year follow-up.<sup>12</sup>

Thyroxine is one of the most frequently prescribed drugs in the United States (almost 120 million prescriptions are dispensed annually)<sup>40</sup> and prescriptions continue to rise, even for individuals with TSH levels <10 mIU/L.<sup>41</sup> Although our primary analyses focused on endogenous thyroid function, we also examined thyroxine users in stratified analyses. These results remained consistent with higher AF risk with increasing fT4 levels; our data also showed that the majority of thyroxine users had a fT4 level in the highest quartile. However, the subgroup of individuals on thyroid replacement therapy at baseline was comparatively small in our study (n=1146), which precludes a meaningful interpretation

of the AF risk associated with thyroxine therapy. Further studies are needed to evaluate whether our findings apply to this subgroup.

Our study has several limitations. First, we did not prespecify our analysis of the association between fT4 and AF risk in the protocol; because 2 prospective cohorts, published after we completed our protocol, found a significant association between fT4 in the euthyroid range and incident AF,<sup>14,24</sup> we decided to explore AF risk according to fT4 levels. Our robust results have confirmed these previous findings. Second, AF can be paroxysmal or asymptomatic, and the real incident date for AF might have been missed in the cohorts that diagnosed AF solely by ECG review during study visits. Therefore, we might have substantially underestimated the true incidence of AF in our study and introduced nondifferential misclassification of outcomes, which would result in an underestimation of the association. Third, only 5 of the included studies provided data on follow-up thyroid function measurements, so data on the evolution of thyroid function over time were limited, which applies to most published large cohorts.<sup>13,16,25</sup> This limitation mainly affects the analysis of individuals with subclinical hypothyroidism, who might reverse to normal thyroid function or progress to overt thyroid dysfunction. However, a sensitivity analysis including only participants with persistent thyroid function during follow-up thyroid function measurements yielded similar estimates. Fourth, despite the large number of individuals we included in our analysis, important subgroups of interest (such as participants with high TSH levels or individuals on thyroxine therapy at baseline) were small, and analyses restricted to these subgroups were underpowered. Fifth, we could not obtain IPD from 2 studies that met our inclusion criteria. Therefore, we performed sensitivity analyses adding the published aggregate results from these 2 studies,<sup>9,24</sup> which yielded similar results. We could not add the aggregate results of the association between TSH in the reference range and AF published in the study by Chaker and colleagues,<sup>24</sup> because they used different TSH cutoffs by subdividing TSH into quartiles. Sixth, we were not able to include time-updated variables in our analyses because of limited availability. Seventh, the definition of some of the baseline covariates including cardiovascular disease and diabetes mellitus was heterogeneous across different cohorts. Finally, our study included mainly white subjects and younger participants were few (median age, 69 y), which reduces the generalizability of our findings to other populations.

The mechanism for the association between thyroid function and AF may be explained by the effects of thyroid hormones on the cardiovascular system. Thyroid function in the high range leads to an increase in vascular resistance, cardiac contractility, heart rate, and left ventricular mass.<sup>42</sup> Thyroid hormone levels in the high

range have been shown to be arrhythmogenic<sup>43</sup> and increase the frequency of atrial premature beats,<sup>44</sup> which in turn is a risk factor for AF.<sup>45</sup> These effects may explain the observation of an increased risk of AF in subclinical hyperthyroidism<sup>8</sup> but not subclinical hypothyroidism. Because of the negative feedback, a negative log-linear relationship exists between fT4 and TSH with disproportionately larger changes in TSH concentrations than those of fT4.<sup>46</sup> Therefore, TSH would be expected to be more sensitive than fT4 to predict outcomes. However, circulating fT4 is peripherally converted to the biologically active triiodothyronine, which binds on nuclear receptors and mediates gene expression with consecutive effects on end-organs, whereas TSH is a marker of pituitary effects of thyroid function.<sup>47</sup> In contrast to the positive association between fT4 and AF, we did not find an association between TSH levels in the reference range and AF, and this pattern of a positive association between fT4 but not TSH values in the reference range has also been shown for other adverse cardiac outcomes including congestive heart failure<sup>14</sup> and sudden cardiac death,<sup>15</sup> and for blood pressure, as well.<sup>48</sup> These results of the effect of normal thyroid function on the heart are in contrast to the findings of a statistically significant inverse association between TSH levels within the reference range and dementia, whereas no significant association between fT4 levels in the normal range and rates of dementia was found in this study,<sup>14</sup> suggesting that thyroid hormone metabolism and action differ between target organs such as the heart and brain because of differences in deiodinase activity and thyroid hormone receptor expression<sup>47</sup>; these differences may explain why some clinical phenotypes are associated with fT4 only, some with TSH only, and others with both. These findings are also consistent with the observation that fT4 concentrations may differ even among euthyroid persons with the same TSH values<sup>49</sup>: individuals with higher fT4 values have higher cardiac exposure to thyroid hormones and are consecutively at a higher risk of AF, which is reflected by the findings of our study. Levels of fT4 might be an additive risk factor for adverse cardiac outcomes; however, before making recommendations for fT4 screening in euthyroid individuals, further (ideally, randomized) studies are needed to assess the benefits and harms of fT4 screening.

In conclusion, our IPD analysis of prospective cohorts showed that fT4 levels within the high-normal range were associated with increased risk of incident AF, but incident AF events did not increase across TSH categories within the euthyroid range or in subclinical hypothyroidism. Further studies are needed to investigate whether these results apply to thyroxine users, which might entail a careful evaluation of the risks and benefits of current target thyroid hormone concentrations for thyroid replacement therapy.

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## DISCLOSURES

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## FOOTNOTES

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