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## Subclinical Hyperthyroidism and the Risk of Coronary Heart Disease and Mortality

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## Abstract

**Background**—Data from prospective cohort studies regarding the association between subclinical hyperthyroidism and cardiovascular outcomes are conflicting. We aimed to assess the risks of total and coronary heart disease (CHD) mortality, CHD events, and atrial fibrillation (AF) associated with endogenous subclinical hyperthyroidism among all available large prospective cohorts.

**Methods**—Individual data on 52 674 participants were pooled from 10 cohorts. Coronary heart disease events were analyzed in 22 437 participants from 6 cohorts with available data, and incident AF was analyzed in 8711 participants from 5 cohorts. Euthyroidism was defined as thyrotropin level between 0.45 and 4.49 mIU/L and endogenous subclinical hyperthyroidism as thyrotropin level lower than 0.45 mIU/L with normal free thyroxine levels, after excluding those receiving thyroid-altering medications.

**Results**—Of 52 674 participants, 2188 (4.2%) had subclinical hyperthyroidism. During follow-up, 8527 participants died (including 1896 from CHD), 3653 of 22 437 had CHD events, and 785 of 8711 developed AF. In age- and sex-adjusted analyses, subclinical hyperthyroidism was associated with increased total mortality (hazard ratio [HR], 1.24, 95% CI, 1.06–1.46), CHD mortality (HR, 1.29; 95% CI, 1.02–1.62), CHD events (HR, 1.21; 95% CI, 0.99–1.46), and AF (HR, 1.68; 95% CI, 1.16–2.43). Risks did not differ significantly by age, sex, or preexisting cardiovascular disease and were similar after further adjustment for cardiovascular risk factors, with attributable risk of 14.5% for total mortality to 41.5% for AF in those with subclinical hyperthyroidism. Risks for CHD mortality and AF (but not other outcomes) were higher for thyrotropin level lower than 0.10 mIU/L compared with thyrotropin level between 0.10 and 0.44 mIU/L (for both, *P* value for trend, .03).

**Conclusion**—Endogenous subclinical hyperthyroidism is associated with increased risks of total, CHD mortality, and incident AF, with highest risks of CHD mortality and AF when thyrotropin level is lower than 0.10 mIU/L.

Subclinical hyperthyroidism, defined by low thyrotropin level with normal concentrations of free thyroxine (FT<sub>4</sub>) and triiodothyronine (T<sub>3</sub>),<sup>1–4</sup> has been associated with several biological effects on cardiovascular system, such as increased heart rate, left ventricular mass, carotid intimamedia thickness, and plasma fibrinogen levels.<sup>3,5</sup> Observational studies have reported an association between subclinical hyperthyroidism and coronary heart disease (CHD),<sup>6–8</sup> incident atrial fibrillation (AF),<sup>9–12</sup> and cardiac dysfunction.<sup>13,14</sup> Results from prospective cohort studies are conflicting,<sup>6,10</sup> and study-level meta-analyses have reached contradictory conclusions, for example, regarding the association between subclinical hyperthyroidism and cardiovascular mortality.<sup>15–17</sup> In fact, interpretation of these studies is hampered by several methodological factors: population heterogeneity, different thyrotropin cutoff levels for subclinical hyperthyroidism definition, different use of covariates, and different CHD definitions.<sup>16</sup> Although no large randomized controlled trials have examined the effects of treating subclinical hyperthyroidism on clinically relevant outcomes, a consensus statement<sup>2</sup> and recent guidelines<sup>4</sup> advocate treatment of subclinical

hyperthyroidism, particularly when thyrotropin level is lower than 0.10 mIU/L, to avoid long-term complications.

Individual participant data analysis from large cohort studies may help reconcile these conflicting results; allow exploration of the influence of age, sex, thyrotropin levels, and preexisting cardiovascular disease (CVD); and allows the use of a uniform thyrotropin cutoff level and outcome definitions for all participants. This approach is considered optimal for synthesizing evidence across cohorts because it is not subject to potential bias from study-level meta-analyses (ecological fallacy)<sup>18</sup> and allows performance of time-to-event analyses.<sup>19</sup>

On the basis of data from the Thyroid Studies Collaboration,<sup>20</sup> we aimed to assess the risks of total mortality, CHD mortality, CHD events, and AF associated with endogenous subclinical hyperthyroidism.

## METHODS

Similar to our previous study,<sup>20</sup> we conducted a systematic literature search in MEDLINE and EMBASE databases from 1950 to June 30, 2011, without language restriction (eAppendix; <http://www.archinternmed.com>), and screened bibliographies from retrieved articles. We used a priori criteria for greater comparability and quality of the studies. We included only full-text published longitudinal cohorts reporting baseline thyroid function test results (both thyrotropin and FT<sub>4</sub>), with a control euthyroid group and prospective follow-up of mortality and CHD outcomes. We excluded studies that included only participants taking thyroid-altering medications (antithyroid drugs, thyroxine, or amiodarone) or participants with overt hyperthyroidism (low thyrotropin and high FT<sub>4</sub> levels). We performed an additional systematic literature review for articles reporting incident AF events and updated our previous search<sup>20</sup> to June 2011. Reviews were performed independently by 2 authors (P.B. and B.G.), and discrepancies were resolved by discussion with a third author (N.R.). Agreement between reviewers was 99.9% for first screen (titles and abstracts,  $\kappa=0.66$ ; 95% CI, 0.62–0.72) and 100% for full-text screen ( $\kappa=1.00$ ).

Data were collected from original studies that joined the Thyroid Studies Collaboration<sup>20</sup> and included individual demographic characteristics; thyrotropin, FT<sub>4</sub>, and total T<sub>3</sub> or free T<sub>3</sub> levels; baseline cardiovascular risk factors (eg, blood pressure, cigarette smoking, total cholesterol level, diabetes mellitus); preexisting CVD; and cardiovascular and thyroid-altering medication use at baseline and during follow-up. Data on mortality, CHD events, AF, stroke, and cancer outcomes were requested.

Similar to our previous analysis,<sup>20</sup> we used a uniform thyrotropin cutoff level for subclinical hyperthyroidism definition, based on an expert consensus meeting of our collaboration<sup>20</sup> (International Thyroid Conference, Paris, France, 2010), expert reviews,<sup>1,21</sup> and previous large cohorts.<sup>10,22,23</sup> Subclinical hyperthyroidism was defined as a thyrotropin level lower than 0.45 mIU/L with normal FT<sub>4</sub> levels, and euthyroidism as a thyrotropin level between 0.45 and 4.49 mIU/L. Subclinical hyperthyroidism was further categorized as suppressed thyrotropin level (<0.10 mIU/L) and low but not suppressed thyrotropin level (0.10–0.44 mIU/L) according to current guidelines.<sup>1,4</sup> Data from cohorts using first-generation thyrotropin assays (functional sensitivity, 1–2 mIU/L) were excluded<sup>9,24,25</sup> because subclinical hyperthyroidism cannot be diagnosed using these methods.<sup>26</sup> For FT<sub>4</sub> and total and free T<sub>3</sub>, we used study-specific cutoff values because these measurements show greater intermethod variation than thyrotropin assays. For participants with missing values of FT<sub>4</sub> and total or free T<sub>3</sub> (measured in 5 of 10 cohorts [eTable]), we performed sensitivity

analyses excluding (1) participants with missing FT<sub>4</sub> values and (2) those with abnormal total or free T<sub>3</sub> levels.<sup>1-4,21</sup>

Outcomes were total mortality, CHD mortality, CHD events, and incident AF. Stroke and cancer mortality were available for all cohorts except one.<sup>27</sup> As in our previous analysis,<sup>20</sup> we used homogenous definitions to reduce the heterogeneity in outcomes.<sup>15,16</sup> Similar to the Framingham risk score,<sup>28</sup> we limited cardiovascular mortality to CHD mortality or sudden death (eTable). We defined CHD events as nonfatal myocardial infarction or CHD death (equivalent to hard events<sup>28</sup>) or hospitalization for angina or coronary revascularization.<sup>10</sup> We performed a sensitivity analysis with hard CHD events only (ie, CHD death, nonfatal myocardial infarction). For AF analyses, participants with baseline AF were excluded (eTable).

To assess the risks of endogenous subclinical hyperthyroidism, we excluded participants using thyroxine or antithyroid drugs at baseline. To explore the possible heterogeneity between exogenous (using thyroid-altering medications) and endogenous subclinical hyperthyroidism, we performed sensitivity analyses by adding participants using thyroxine or antithyroid drugs at baseline.

We conducted a study quality evaluation using previous criteria<sup>16</sup> after collecting the following additional information from study authors: methods of outcome adjudication and ascertainment, accounting for confounders, and completeness of follow-up.

The association between subclinical hyperthyroidism and each outcome was analyzed using separate Cox proportional hazard models for each cohort (SAS 9.2 [SAS Institute Inc]; Stata 11.2 [StataCorp]). Pooled estimates for each outcome were calculated using random-effects models based on inverse variance model<sup>29</sup> as recommended.<sup>19,30,31</sup> Results were summarized using forest plots (Review Manager 5.1.2, Nordic Cochrane Centre). To assess heterogeneity across studies, we used the I<sup>2</sup> statistic, which measures the inconsistency across studies attributable to heterogeneity instead of chance alone.<sup>32</sup>

Primary analyses were adjusted for age and sex (some traditional cardiovascular risk factors being potential mediators<sup>3</sup>), then further adjusted for traditional cardiovascular risk factors (systolic blood pressure, current or former smoking, total cholesterol, and diabetes). As missing data rates were lower than 3% and unlikely to substantially bias the multivariate model estimates,<sup>33</sup> complete case analysis was used.

To explore potential sources of heterogeneity, we performed predefined subgroup and sensitivity analyses, as in our previous analysis.<sup>20</sup> We conducted stratified analyses by age, sex, race, thyrotropin categories, and preexisting CVD. For strata with participants but no event in some subgroup analyses, we used penalized likelihood methods<sup>34</sup> to calculate hazard ratios (HRs) and 95% confidence intervals. To calculate age- and sex-adjusted event rates/1000 person-years, we used Poisson models.<sup>35</sup> We checked the proportional hazard assumption using graphical methods and the Schoenfeld test.<sup>36</sup> For publication bias, we used age- and sex-adjusted funnel plots and the Egger test.<sup>37</sup>

## RESULTS

Among identified reports, 13 prospective cohorts met all inclusion criteria (eFigure). We excluded 3 cohorts<sup>9,24,25</sup> using first-generation thyrotropin assays,<sup>26</sup> which were insufficiently sensitive for the diagnosis of subclinical hyperthyroidism. After the exclusion of users of thyroxine and antithyroid drugs, the final sample comprised 10 prospective cohorts with a total of 52 674 participants (median age, 59 years, 58.5% women), with median follow-up 8.8 years and total follow-up 501 922 persons-years. Of the participants,

50 486 were euthyroid and 2188 (4.2%) had endogenous subclinical hyperthyroidism (Table 1), including 1884 participants (3.6%) with low but not suppressed thyrotropin (0.10–0.44 mIU/L) and 304 (0.6%) with suppressed thyrotropin (<0.10 mIU/L). The loss to follow-up rate was lower than 5% in all included studies. Total and CHD mortality were reported in all cohorts. Coronary heart disease event data were available for 22 437 participants from 6 cohorts (3.2% with subclinical hyperthyroidism), and were formally adjudicated for 4 of these 6 studies.<sup>7,8,10,38</sup> After excluding those with AF at baseline, data for incident AF events were available in 8711 participants from 5 cohorts (9.3% with subclinical hyperthyroidism).

During follow-up, 8527 participants died (including 1896 from CHD), 3653 had CHD events, and 785 had incident AF. In age- and sex-adjusted analyses, the overall HR for participants with subclinical hyperthyroidism compared with euthyroidism was 1.24 (95% CI, 1.06–1.46; 23.5 vs 19.9/1000 person-years for euthyroidism) for total mortality, 1.29 (95% CI, 1.02–1.62; 5.1 vs 4.5/1000 person-years) for CHD mortality, 1.21 (95% CI, 0.99–1.46; 24.1 vs 20.9/1000 person-years) for CHD events, and 1.68 (95% CI, 1.16–2.43; 17.1 vs 12.5/1000 person-years) for incident AF (Figure). Stroke and cancer mortality were not higher with subclinical hyperthyroidism. Heterogeneity was present across studies for total mortality ( $I^2 = 49\%$ ), but not for CHD mortality, CHD events or incident AF (all  $I^2 = 0\%$ ). Among subclinical hyperthyroid and euthyroid groups, there was a trend for more late events than early events for total mortality, CHD mortality, CHD events, and AF events (for all,  $P$  value for trend, .02). We subsequently examined whether heterogeneity was related to differences in risks by degree of subclinical hyperthyroidism and age.

Table 2 presents stratified analyses for total mortality, CHD mortality, CHD events, and incident AF. In age- and sex-adjusted analyses, CHD mortality and incident AF (but not other outcomes) were significantly greater in participants with lower thyrotropin levels: HRs, 1.24 (95% CI, 0.96–1.61) and 1.63 (95% CI, 1.10–2.41) for thyrotropin levels 0.10–0.44 mIU/L, respectively, vs HRs, 1.84 (95% CI, 1.12–3.00) and 2.54 (95% CI, 1.08–5.99) for thyrotropin levels lower than 0.10 mIU/L, respectively (for both,  $P$  value for trend, .03 for each outcome). Men had a slightly greater risk for total mortality, CHD mortality and incident AF, without statistical significance for interaction (all  $P \geq .30$ ). Risks for Asian participants were greater for total mortality (HR, 2.73; 95% CI, 1.53–4.88) and CHD mortality (HR, 2.35; 95% CI, 0.50–11.14), with nonsignificant interaction test results (all  $P \geq .40$ ), but data on Asian participants were available from only 1 cohort.<sup>40</sup> Risks did not differ significantly by age or preexisting CVD. All risks were similar after further adjustment for cardiovascular risk factors, with an attributable risk of 14.5% for total mortality to 41.5% for AF in those with subclinical hyperthyroidism and a population attributable risk of 0.7% for total mortality to 6.2% for AF, given the relatively low prevalence of subclinical hyperthyroidism.

Sensitivity analyses yielded similar results (Table 3). Excluding users of thyroxine and antithyroid drugs during follow-up or adding participants taking these medications at baseline to the overall sample yielded similar HRs. The risk of CHD mortality was higher (HR, 1.50; 95% CI, 1.00–2.27) after limiting the analyses to 4 studies with formal adjudication procedures.<sup>7,8,13,38</sup> Risks of total mortality, CHD mortality and incident AF increased slightly after excluding a study with previous iodine supplementation.<sup>39</sup> Risks were similar after further adjustment of multivariate models with lipid-lowering and antihypertensive medication use or body mass index.

The proportional hazard assumption was consistent across studies, except for the Birmingham Study<sup>6</sup> ( $P = .009$ ), which was excluded in a sensitivity analysis giving similar results. We found limited evidence of publication bias with visual assessment of age- and

sex-adjusted funnel plots and the Egger test for total mortality ( $P = .17$ ), but not the other outcomes (all  $P \geq .20$ ). For total mortality, the Brazilian Thyroid Study<sup>40</sup> might be an outlier with no corresponding study of similar size with reduced risk associated with subclinical hyperthyroidism: a sensitivity analysis excluding this study yielded similar results.

## COMMENT

In this analysis of all available prospective cohorts, endogenous subclinical hyperthyroidism was associated with an increased risk of total mortality, CHD mortality, and incident AF. Coronary heart disease mortality and incident AF (but not other outcomes) were significantly greater in participants with thyrotropin levels lower than 0.10 mIU/L than those with thyrotropin levels between 0.10 and 0.44 mIU/L (for both,  $P$  value for trend,  $.03$ ). Risks did not differ significantly by age, sex, or preexisting CVD and were similar after further adjustment for cardiovascular risk factors.

Previous study-level meta-analyses produced conflicting results regarding the association between subclinical hyperthyroidism and cardiovascular mortality.<sup>15–17</sup> Our results, based on individual participant data, demonstrate that there is indeed an increased risk of total and CHD mortality associated with subclinical hyperthyroidism,<sup>15,16</sup> and add new information on subgroups at increased risk and the risk of incident AF. Previous meta-analyses could not accurately assess the differences in risk according to thyrotropin level, because of potential ecological fallacy without individual participant data analysis<sup>18</sup> and they pooled individual studies using varying thyrotropin cutoff levels, outcome definitions, and confounding factors for adjustment.<sup>15,16</sup> Only a few individual studies reported stratified risks according to thyrotropin levels. Our results are consistent with those recently reported by Vadiveloo et al,<sup>41</sup> who found an increased risk of nonfatal CVD, increasing with lower thyrotropin levels (HR, 1.67 [95% CI, 1.45–1.92] for thyrotropin level 0.10–0.40 mIU/L, vs HR, 1.74 [95% CI, 1.36–2.21] for thyrotropin level <0.10 mIU/L); this study was not included in our analysis because of its retrospective case-control design.

To our knowledge, no meta-analysis has been conducted on the association of AF with subclinical hyperthyroidism. Similar to our data, some individual studies showed increased risk of AF associated with subclinical hyperthyroidism.<sup>9,10</sup> Sawin et al<sup>9</sup> reported an increased risk of incident AF in persons older than 60 years with thyrotropin levels lower than 0.1 mIU/L (HR, 3.8; 95% CI, 1.7–8.3) and among those with thyrotropin levels between 0.1 and 0.4 mIU/L (HR, 1.6; 95% CI, 1.0–2.5); this study was excluded from our analysis because of its first-generation thyrotropin assay.<sup>26</sup> Cappola et al<sup>10</sup> showed a relationship between low thyrotropin levels and AF incidence in individuals 65 years or older with endogenous subclinical hyperthyroidism, which was also significant in those with thyrotropin levels between 0.10 and 0.44 mIU/L (HR, 1.85; 95% CI, 1.14–3.00). In a population with a mean age of 65.5 years, Vadiveloo et al<sup>41</sup> found an increased risk of cardiac arrhythmia for participants with endogenous subclinical hyperthyroidism, especially in those with thyrotropin levels lower than 0.10 mIU/L. Taken together, these previous studies and our data suggest that the risk of AF in individuals with endogenous subclinical hyperthyroidism is higher with lower thyrotropin levels and is mostly pronounced in those with thyrotropin levels lower than 0.10 mIU/L.

The increased risks of AF events and total and CHD mortality associated with subclinical hyperthyroidism have been postulated to be caused by systemic effects of thyroid hormones, such as a change in cardiac function<sup>1,3</sup> or cardiac arrhythmia.<sup>3,42</sup> These hypotheses are favored by the fact that adjustment for cardiovascular risk factors did not alter risks of subclinical hyperthyroidism. An alternative explanation for the results could be publication bias, selection bias or quality issues in the included cohorts, or unmeasured confounders.<sup>43</sup>

Sensitivity analyses (1) excluding a small study<sup>40</sup> with no corresponding study of similar size with reduced risk associated with subclinical hyperthyroidism and (2) pooling only higher-quality cohorts yielded similar results.

Among the strengths of our study, an individual participant data analysis is considered the best way for synthesizing evidence across several studies because it is not subject to potential bias from study-level meta-analyses (ecological fallacy)<sup>18</sup> and allows performance of time-to-event analyses and use of standardized definitions of predictors, outcomes, and adjustment for confounding factors.<sup>19</sup> We included all available international published data after conducting a systematic review.

Among the limitations of our study, our analysis included predominantly white populations, except for one cohort including Brazilians of Japanese descent.<sup>40</sup> Although we included all available data, our results may not be generalized to all other populations. Second, thyroid function tests were performed only at baseline, and we have no data to assess how many participants with subclinical hyperthyroidism progressed to overt hyperthyroidism or normalized to euthyroidism over time, which is a limitation of most published large cohorts.<sup>10,23,27,38</sup> Third, subclinical hyperthyroidism was defined as a thyrotropin level lower than 0.45 mIU/L and normal FT<sub>4</sub> levels, since T<sub>3</sub> was not measured in all included cohorts; sensitivity analyses excluding participants with abnormal total or free T<sub>3</sub> levels yielded similar results. Fourth, the high prevalence of subclinical hyperthyroidism in the Study of Health in Pomerania (SHIP, Northern Germany, 24.1%) may be explained by the iodine supplementation that was introduced in the area 4 years before the start of SHIP in the late 1990s.<sup>44</sup> Excluding SHIP yielded similar risk estimates. Fifth, we did not have information on the etiology of subclinical hyperthyroidism, while cardiovascular complications may be related to the etiology of the condition.<sup>45</sup> Sixth, up to 2.6% of participants started thyroxine or antithyroid drugs during follow-up; sensitivity analyses excluding users of these medications during follow-up yielded similar results. However, we did not have complete data from all cohorts on use of other medications that could alter thyrotropin and/or FT<sub>4</sub> levels, such as steroids or amiodarone; sensitivity analyses excluding other medications users (0%–2.8% when available) yielded similar results. Seventh, only mortality and cardiovascular outcomes were assessed. Other conditions such as osteoporosis and cognition were not analyzed and could partly account for increased total mortality, particularly among elderly persons, although data on the associations between subclinical hyperthyroidism and osteoporosis and cognition are conflicting.<sup>1</sup> Eighth, 4 of 6 studies<sup>7,8,10,38</sup> formally adjudicated CHD outcomes. Sensitivity analyses limited to these 4 studies yielded similar risk estimates. As most included cohorts used self-reported preexisting CVD, stratified analyses according to preexisting CVD should be interpreted with caution.

Recent guidelines<sup>4</sup> recommend that “treatment of SH [subclinical hyperthyroidism] should be strongly considered in all individuals > 65 years of age” with thyrotropin level lower than 0.10 mIU/L (recommendation 65) and “treatment of SH should be considered in individuals > 65 years of age” with low thyrotropin levels but 0.1 mIU/L or higher (recommendation 66). Based on all available prospective cohort studies, our findings of increased risks of total mortality, CHD mortality, and incident AF associated with subclinical hyperthyroidism, with greater risks of CHD mortality and AF among those with thyrotropin levels lower than 0.10 mIU/L, are consistent with these recent guidelines.<sup>4</sup> However, findings based on observational data should be interpreted with great caution for clinical practice, since they are subject to several aforementioned limitations. No clinical trials have assessed whether treating subclinical hyperthyroidism results in improved cardiovascular outcomes. Because our data included only a limited sample of young men and premenopausal women, generalization of our findings to younger adults is limited.

In conclusion, pooling individual data from all available prospective cohorts suggests that endogenous subclinical hyperthyroidism is associated with an increased risk of total mortality, CHD mortality, and incident AF, with higher risks of CHD mortality and AF with thyrotropin levels below 0.10 mIU/L. Our study is observational, and as such cannot address whether the risks associated with subclinical hyperthyroidism are lowered by treatment. A large randomized controlled trial with relevant clinical outcomes will be required to demonstrate whether these risks are altered by therapy; such a trial will be challenging to conduct given the large sample size required and the lower prevalence of adults with subclinical hyperthyroidism compared with subclinical hypothyroidism. If conducted, such a trial should examine prevention of AF and surrogate outcome measures, such as carotid intima-media thickness.<sup>46</sup>

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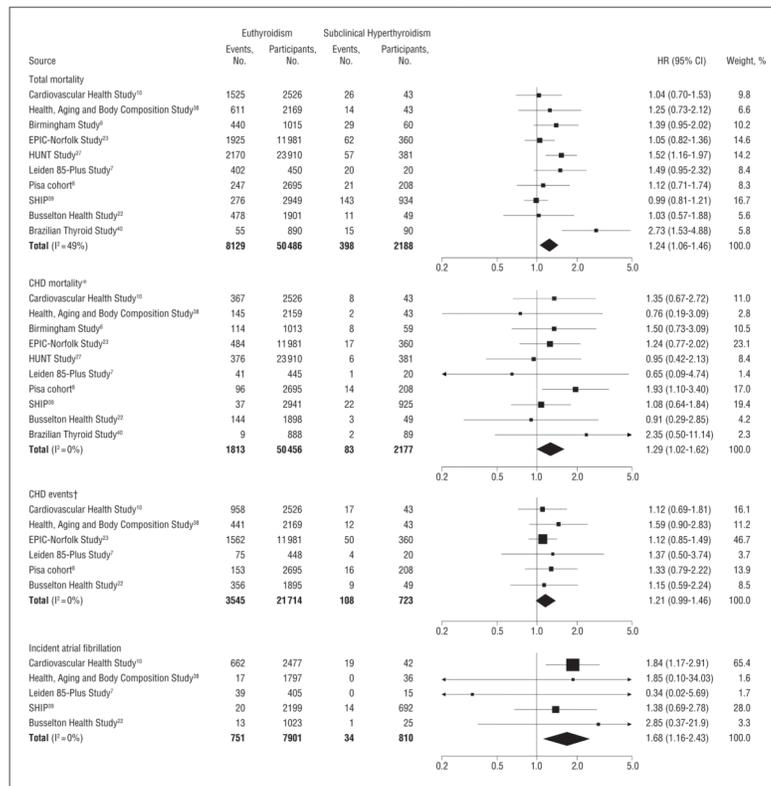
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**Figure.**

Total mortality, coronary heart disease (CHD) mortality, CHD events, and atrial fibrillation in endogenous subclinical hyperthyroidism vs euthyroidism. Age and sex-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) are represented by squares or diamonds, those to the right of the solid line indicate increased risk. The sizes of data markers are proportional to the inverse of the variance of the HRs. \*Forty-one participants were excluded from the analyses of CHD mortality because of missing cause of death. †The Birmingham Study,<sup>6</sup> HUNT (Nord-Trøndelag Health Study),<sup>27</sup> SHIP (Study of Health in Pomerania),<sup>39</sup> and Brazilian Thyroid Study<sup>40</sup> were not included because follow-up data were only available for death. EPIC indicates European Prospective Investigation of Cancer.

Table 1

## Baseline Characteristics of Individuals in Included Studies

| Source                                    | Description of Study Sample                                                           | No. of Participants | Age, Median (Range), y <sup>a</sup> | Women                | Endogenous Subclinical Hypert thyroidism <sup>b</sup> | Thyroid Medication During Follow-up <sup>c</sup> | Follow-up <sup>d</sup> |                       |                        |
|-------------------------------------------|---------------------------------------------------------------------------------------|---------------------|-------------------------------------|----------------------|-------------------------------------------------------|--------------------------------------------------|------------------------|-----------------------|------------------------|
|                                           |                                                                                       |                     |                                     |                      |                                                       |                                                  | No. (%)                | Start                 | Duration, Median (IQR) |
| United States                             |                                                                                       |                     |                                     |                      |                                                       |                                                  |                        |                       |                        |
| Cardiovascular Health Study <sup>10</sup> | Community-dwelling adults with Medicare eligibility in 4 US communities               | 2569                | 71 (64–100)                         | 1516 (59.0)          | 43 (1.7)                                              | 57 (2.2)                                         | 1989–1990              | 14.0 (8.6–16.4)       | 31 599                 |
| Health, ABC Study <sup>38</sup>           | Community-dwelling adults with Medicare eligibility in 2 US communities               | 2212                | 74 (70–79)                          | 1062 (48.0)          | 43 (1.9)                                              | 43 (1.9)                                         | 1997                   | 8.1 (7.2–8.3)         | 15 772                 |
| Europe                                    |                                                                                       |                     |                                     |                      |                                                       |                                                  |                        |                       |                        |
| Birmingham Study <sup>6</sup>             | Community-dwelling adults aged 60 y from primary care practice in Birmingham, England | 1075                | 69 (60–94)                          | 586 (54.5)           | 60 (5.6)                                              | 5 (0.5)                                          | 1988                   | 10.2 (5.5–10.6)       | 8688                   |
| EPIC-Norfolk Study <sup>23</sup>          | Adults living in Norfolk, England                                                     | 12 341              | 58 (40–78)                          | 6596 (53.4)          | 360 (2.9)                                             | NA                                               | 1995–1998              | 13.4 (12.6–14.3)      | 158 227                |
| HUNT Study <sup>27</sup>                  | Adults living in Nord-Trøndelag County, Norway                                        | 24 291              | 55 (41–98)                          | 16 506 (68.0)        | 381 (1.6)                                             | NA                                               | 1995–1997              | 8.3 (7.9–8.9)         | 197 935                |
| Leiden 85-Plus Study <sup>7</sup>         | All adults aged 85 y living in Leiden, the Netherlands                                | 470                 | 85                                  | 301 (64.0)           | 20 (4.3)                                              | 12 (2.6)                                         | 1997–1999              | 5.2 (2.6–8.5)         | 2650                   |
| Pisa cohort <sup>8</sup>                  | Patients admitted to the cardiology department in Pisa, Italy <sup>e</sup>            | 2903                | 63 (19–92)                          | 927 (31.9)           | 208 (7.2)                                             | 0                                                | 2000–2005              | 2.6 (1.6–3.8)         | 7966                   |
| SHIP <sup>39</sup>                        | Adults living in Western Pomerania, Germany                                           | 3883                | 49 (20–81)                          | 1891 (48.7)          | 934 (24.1)                                            | 140 (3.6)                                        | 1997–2001              | 10.1 (9.3–10.7)       | 37 532                 |
| Australia                                 |                                                                                       |                     |                                     |                      |                                                       |                                                  |                        |                       |                        |
| Busselton Health Study <sup>22</sup>      | Adults living in Busselton, Western Australia                                         | 1950                | 51 (18–90)                          | 933 (47.8)           | 49 (2.5)                                              | 12 (0.6)                                         | 1981                   | 20.0 (20.0–20.0)      | 34 676                 |
| South America                             |                                                                                       |                     |                                     |                      |                                                       |                                                  |                        |                       |                        |
| Brazilian Thyroid Study <sup>40</sup>     | Adults of Japanese descent living in São Paulo, Brazil                                | 980                 | 57 (30–92)                          | 510 (52.0)           | 90 (9.2)                                              | NA                                               | 1999–2000              | 7.3 (7.0–7.5)         | 6877                   |
| <b>Overall</b>                            |                                                                                       | <b>52 674</b>       | <b>59 (18–100)</b>                  | <b>30 828 (58.5)</b> | <b>2188 (4.2)</b>                                     | <b>269 (0.5)</b>                                 | <b>1981–2005</b>       | <b>8.8 (7.9–12.4)</b> | <b>501 922</b>         |

Abbreviations: EPIC, European Prospective Investigation of Cancer; Health ABC Study, Health Aging and Body Composition Study; HUNT, Nord-Trøndelag Health Study; IQR, interquartile range (25th–75th percentiles); NA, data not available; SHIP, Study of Health in Pomerania.

<sup>a</sup>Participants younger than 18 years were excluded.

<sup>b</sup> We used a common definition of subclinical hyperthyroidism, thyrotropin level lower than 0.45 mIU/L, and normal free thyroxine level, whereas thyrotropin cutoff values varied among the previous reports from each cohort, resulting in different numbers from previous reports. For endogenous subclinical hyperthyroidism, 216 participants of Health ABC Study, 9 of Leiden 85-Plus Study, 258 of SHIP, and 14 of Busselton Health Study were excluded because of thyroid medication use at baseline.

<sup>c</sup> Data on thyroid medication use (thyroxine, antithyroid drugs) were not available for 8 participants of the Health ABC Study at baseline, for 1006 participants of Birmingham Study during follow-up, and for all participants during follow-up in EPIC-Norfolk Study, HUNT Study, and Brazilian Thyroid Study.

<sup>d</sup> For all cohorts, we used the maximal follow-up data that were available, which might differ from previous reports for some cohorts.

<sup>e</sup> Patients with acute coronary syndrome or severe illness were excluded from the Pisa cohort.

**Table 2**  
Stratified Analyses for the Association Between Endogenous Subclinical Hyperthyroidism and the Risk of Total Mortality, CHD Mortality, CHD Events, and Atrial Fibrillation

| Variable                       | Total Mortality          |                             |                          |                                 | CHD Mortality <sup>b</sup> |                             |                          |                                 |
|--------------------------------|--------------------------|-----------------------------|--------------------------|---------------------------------|----------------------------|-----------------------------|--------------------------|---------------------------------|
|                                | Events/Participants, No. | HR (95% CI)                 | Events/Participants, No. | HR (95% CI)                     | Events/Participants, No.   | HR (95% CI)                 | Events/Participants, No. | HR (95% CI)                     |
|                                | Enthyroidism             | Subclinical Hyperthyroidism | Age/Sex-Adjusted         | Multivariate Model <sup>a</sup> | Enthyroidism               | Subclinical Hyperthyroidism | Age/Sex-Adjusted         | Multivariate Model <sup>a</sup> |
| Total population               | 8129/50 486              | 398/2188                    | 1.24 (1.06–1.46)         | 1.17 (0.99–1.38)                | 1813/50 456                | 83/2177                     | 1.29 (1.02–1.62)         | 1.25 (0.97–1.62)                |
| Sex                            |                          |                             |                          |                                 |                            |                             |                          |                                 |
| Men                            | 4156/20 887              | 216/959                     | 1.28 (1.10–1.49)         | 1.23 (1.05–1.44)                | 1069/20 869                | 50/952                      | 1.52 (1.12–2.08)         | 1.49 (1.07–2.08)                |
| Women                          | 3973/29 599              | 182/1229                    | 1.12 (0.91–1.40)         | 1.05 (0.81–1.35)                | 744/29 587                 | 33/1225                     | 1.22 (0.86–1.72)         | 1.14 (0.78–1.68)                |
| <i>P</i> value for interaction |                          |                             | .31                      | .31                             |                            |                             | .35                      | .30                             |
| Age, y <sup>c</sup>            |                          |                             |                          |                                 |                            |                             |                          |                                 |
| 18–49                          | 254/13 819               | 15/587                      | 1.55 (0.90–2.67)         | 1.70 (0.98–2.96)                | 31/13 817                  | 3/587                       | 5.01 (1.55–16.19)        | 4.24 (1.09–16.42)               |
| 50–64                          | 1210/17 890 <sup>d</sup> | 64/729 <sup>d</sup>         | 1.29 (0.87–1.91)         | 1.24 (0.85–1.80)                | 236/17 885 <sup>d</sup>    | 7/728 <sup>d</sup>          | 1.08 (0.52–2.23)         | 1.02 (0.47–2.18)                |
| 65–79                          | 5101/16 505              | 262/797                     | 1.25 (1.04–1.50)         | 1.12 (0.96–1.32)                | 1254/16 487                | 65/787                      | 1.45 (1.11–1.89)         | 1.40 (1.05–1.88)                |
| 80                             | 1561/2268                | 57/75                       | 1.23 (0.94–1.61)         | 1.14 (0.85–1.52)                | 292/2236 <sup>d</sup>      | 8/73 <sup>d</sup>           | 1.16 (0.58–2.30)         | 0.79 (0.34–1.84)                |
| <i>P</i> value for trend       |                          |                             | .45                      | .18                             |                            |                             | .05                      | .06                             |
| Race <sup>e</sup>              |                          |                             |                          |                                 |                            |                             |                          |                                 |
| White                          | 7221/47 492              | 344/2015                    | 1.15 (1.00–1.31)         | 1.10 (0.98–1.24)                | 1593/47 471                | 72/2006                     | 1.26 (0.98–1.62)         | 1.26 (0.97–1.63)                |
| Black                          | 413/1089                 | 10/23                       | 1.65 (0.72–3.80)         | 1.30 (0.69–2.45)                | 97/1084                    | 1/23                        | 0.96 (0.18–5.11)         | 0.68 (0.12–3.79)                |
| Asian                          | 55/890                   | 15/90                       | 2.73 (1.53–4.88)         | 2.57 (1.43–4.62)                | 9/888                      | 2/89                        | 2.35 (0.50–11.14)        | 2.08 (0.43–10.09)               |
| <i>P</i> for interaction       |                          |                             | .40                      | .61                             |                            |                             | .75                      | .49                             |
| Thyrotropin                    |                          |                             |                          |                                 |                            |                             |                          |                                 |
| 0.45–4.49 mIU/L                | 8129/50 486              |                             | 1 [Reference]            | 1 [Reference]                   | 1813/50 456                |                             | 1 [Reference]            | 1 [Reference]                   |
| 0.10–0.44 mIU/L                |                          | 335/1884                    | 1.23 (1.04–1.45)         | 1.19 (1.00–1.41)                |                            | 68/1875                     | 1.24 (0.96–1.61)         | 1.27 (0.97–1.67)                |
| <0.10 mIU/L                    |                          | 63/304                      | 1.24 (0.90–1.71)         | 1.06 (0.72–1.56)                |                            | 15/302                      | 1.84 (1.12–3.00)         | 1.53 (0.85–2.77)                |
| <i>P</i> value for trend       |                          |                             | .19                      | .77                             |                            |                             | .02                      | .16                             |
| Preexisting CVD <sup>f</sup>   |                          |                             |                          |                                 |                            |                             |                          |                                 |
| None                           | 6361/45 505              | 296/1880                    | 1.26 (1.01–1.58)         | 1.19 (0.97–1.45)                | 1229/45 481                | 52/1872                     | 1.25 (0.93–1.69)         | 1.27 (0.94–1.72)                |
| Yes                            | 1315/3933                | 72/247                      | 1.28 (0.96–1.70)         | 1.14 (0.82–1.59)                | 466/3929                   | 23/245                      | 1.54 (1.00–2.39)         | 1.49 (0.91–2.44)                |
| <i>P</i> value for interaction |                          |                             | .93                      | .83                             |                            |                             | .44                      | .59                             |

| Variable                       | Total Mortality          |                             |                   |                                 | CHD Mortality <sup>b</sup> |                             |                               |                                 |
|--------------------------------|--------------------------|-----------------------------|-------------------|---------------------------------|----------------------------|-----------------------------|-------------------------------|---------------------------------|
|                                | Events/Participants, No. |                             | HR (95% CI)       |                                 | Events/Participants, No.   |                             | HR (95% CI)                   |                                 |
|                                | Euthyroidism             | Subclinical Hyperthyroidism | Age/Sex-Adjusted  | Multivariate Model <sup>f</sup> | Euthyroidism               | Subclinical Hyperthyroidism | Age/Sex-Adjusted              | Multivariate Model <sup>f</sup> |
| Total population               | 3545/21 714              | 108/723                     | 1.21 (0.99–1.46)  | 1.22 (1.00–1.48)                | 751/7901                   | 34/810                      | 1.68 (1.16–2.43)              | 1.71 (1.18–2.48)                |
| Sex                            |                          |                             |                   |                                 |                            |                             |                               |                                 |
| Men                            | 2181/10 792              | 49/313                      | 1.10 (0.83–1.47)  | 1.08 (0.80–1.45)                | 376/3689                   | 19/404                      | 1.79 (1.10–2.91)              | 1.96 (1.19–3.21)                |
| Women                          | 1364/10 922              | 59/410                      | 1.38 (1.06–1.79)  | 1.42 (1.09–1.85)                | 375/4212                   | 15/406                      | 1.71 (0.98–2.96)              | 1.61 (0.92–2.81)                |
| <i>P</i> value for interaction |                          |                             | .25               | .18                             |                            |                             | .90                           | .61                             |
| Age, y <sup>c</sup>            |                          |                             |                   |                                 |                            |                             |                               |                                 |
| 18–49                          | 114/4112                 | 6/122                       | 2.49 (0.46–13.44) | 2.41 (0.43–13.46)               | 2/1261 <sup>d</sup>        | 1/269 <sup>d</sup>          | 1.48 (0.13–16.90)             | 1.19 (0.06–23.40)               |
| 50–64                          | 816/7344 <sup>d</sup>    | 18/261 <sup>d</sup>         | 0.78 (0.49–1.26)  | 0.81 (0.50–1.29)                | 15/966 <sup>d</sup>        | 5/249 <sup>d</sup>          | 2.12 (0.44–10.26)             | 2.25 (0.49–10.35)               |
| 65–79                          | 2362/9286                | 77/305                      | 1.41 (1.12–1.77)  | 1.38 (1.09–1.74)                | 595/4284                   | 23/249                      | 1.80 (1.15–2.83)              | 1.79 (1.13–2.84)                |
| 80                             | 253/968                  | 7/35                        | 1.00 (0.49–2.03)  | 1.06 (0.52–2.19)                | 138/713 <sup>d</sup>       | 5/24 <sup>d</sup>           | 1.35 (0.42–4.35)              | 1.11 (0.45–2.70)                |
| <i>P</i> value for trend       |                          |                             | .45               | .50                             |                            |                             | .92                           | .93                             |
| Race <sup>e</sup>              |                          |                             |                   |                                 |                            |                             |                               |                                 |
| White                          | 3305/20 625              | 102/700                     | 1.19 (0.98–1.46)  | 1.21 (0.99–1.49)                | 727/7013                   | 34/790                      | 1.69 (1.17–2.45)              | 1.74 (1.20–2.52)                |
| Black                          | 240/1089                 | 6/23                        | 1.52 (0.69–3.32)  | 1.43 (0.65–3.16)                | 24/888                     | 0/20                        | NA                            | NA                              |
| Asian                          | NA                       | NA                          | NA                | NA                              | NA                         | NA                          | NA                            | NA                              |
| <i>P</i> value for interaction |                          |                             | .56               | .69                             |                            |                             | NA                            | NA                              |
| Thyrotropin                    |                          |                             |                   |                                 |                            |                             |                               |                                 |
| 0.45–4.49 mIU/L                | 3545/21 714              |                             | 1 [Reference]     | 1 [Reference]                   | 751/7901                   |                             | 1 [Reference]                 | 1 [Reference]                   |
| 0.10–0.44 mIU/L                |                          | 89/572                      | 1.27 (1.03–1.58)  | 1.29 (1.04–1.62)                |                            | 30/735                      | 1.63 (1.10–2.41)              | 1.70 (1.15–2.53)                |
| <0.10 mIU/L                    |                          | 19/151                      | 1.08 (0.69–1.69)  | 1.13 (0.71–1.79)                |                            | 4/75                        | 2.54 (1.08–5.99)              | 2.34 (0.98–5.58)                |
| <i>P</i> value for trend       |                          |                             | .74               | .61                             |                            |                             | .03                           | .06                             |
| Preexisting CVD <sup>g</sup>   |                          |                             |                   |                                 |                            |                             |                               |                                 |
| None                           | 2492/18 022              | 79/554                      | 1.32 (1.05–1.65)  | 1.32 (1.05–1.66)                | 545/6633                   | 27/746                      | 1.78 (1.16–2.74)              | 1.78 (1.16–2.75)                |
| Yes                            | 1044/3661                | 29/168                      | 1.06 (0.73–1.54)  | 1.15 (0.78–1.68)                | 201/1205 <sup>d</sup>      | 7/64 <sup>d</sup>           | 1.44 (0.46–4.58) <sup>d</sup> | 2.05 (0.98–4.32) <sup>d</sup>   |
| <i>P</i> value for interaction |                          |                             | .33               | .55                             |                            |                             | .73                           | .75                             |

Abbreviations: AF, atrial fibrillation; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; NA, data not applicable.

- <sup>a</sup> Adjusted for age, sex, systolic blood pressure, current and former smoking, total cholesterol, and diabetes at baseline. The Birmingham Study was not included in this analysis because of lack of data on cardiovascular risk factors.
- <sup>b</sup> Forty-one participants were excluded from the analyses of CHD mortality because of missing cause of death.
- <sup>c</sup> These HRs were adjusted for sex and age as a continuous variable to avoid residual confounding within age strata.
- <sup>d</sup> Some strata from specific studies were excluded when there was no event in a subgroup.
- <sup>e</sup> Data on race were not available for the Birmingham study (n = 1075). The Asian group was only from the Brazilian (of Japanese descent) Thyroid Study.
- <sup>f</sup> Data on previous CVD were not available for the Birmingham study (n = 1075) and for 34 participants of EPIC (European Prospective Investigation of Cancer)–Norfolk Study, Leiden 85-Plus Study, and Busseton Health Study. For analysis of CHD events, 32 participants of EPIC–Norfolk Study and Busseton Health Study were excluded for the same reason.
- <sup>g</sup> The Birmingham Study, HUNT Study (Nord-Trøndelag Health Study), SHIP (Study of Health in Pomerania), and Brazilian Thyroid Study were not included because follow-up data were only available for death.
- <sup>h</sup> Participants with preexisting AF at baseline or missing data on AF during follow-up were excluded: CHS (Cardiovascular Health Study), 50 and 0, respectively; Health ABC (Aging and Body Composition) Study, 38 and 341, respectively; Leiden-85-Plus Study, 48 and 2 respectively; SHIP, 44 and 948, respectively; and Busseton Health Study, 11 and 891, respectively.

**Table 3**  
Sensitivity Analyses of the Association Between Subclinical Hyperthyroidism and the Risk of Total Mortality, CHD Mortality, CHD Events, and Atrial Fibrillation

| Variable                                                                                                                            | Total Mortality          |                             |                  |                             | CHD Mortality            |                             |             |                             | CHD Events               |                             |             |                             | Incident AF              |                             |             |                             |
|-------------------------------------------------------------------------------------------------------------------------------------|--------------------------|-----------------------------|------------------|-----------------------------|--------------------------|-----------------------------|-------------|-----------------------------|--------------------------|-----------------------------|-------------|-----------------------------|--------------------------|-----------------------------|-------------|-----------------------------|
|                                                                                                                                     | Events/Participants, No. |                             | HR (95% CI)      | Subclinical Hyperthyroidism | Events/Participants, No. |                             | HR (95% CI) | Subclinical Hyperthyroidism | Events/Participants, No. |                             | HR (95% CI) | Subclinical Hyperthyroidism | Events/Participants, No. |                             | HR (95% CI) | Subclinical Hyperthyroidism |
|                                                                                                                                     | Euthyroidism             | Subclinical Hyperthyroidism |                  |                             | Euthyroidism             | Subclinical Hyperthyroidism |             |                             | Euthyroidism             | Subclinical Hyperthyroidism |             |                             | Euthyroidism             | Subclinical Hyperthyroidism |             |                             |
| All eligible studies                                                                                                                |                          |                             |                  |                             |                          |                             |             |                             |                          |                             |             |                             |                          |                             |             |                             |
| Random-effects model                                                                                                                | 8129/50 486              | 398/2188                    | 1.24 (1.06–1.46) | 1813/50 456                 | 83/2177                  | 1.29 (1.02–1.62)            | 3545/21 714 | 108/723                     | 1.21 (0.99–1.46)         | 751/7901                    | 34/810      | 1.68 (1.16–2.43)            |                          |                             |             |                             |
| Fixed-effects model                                                                                                                 | 8129/50 486              | 398/2188                    | 1.19 (1.07–1.33) | 1813/50 456                 | 83/2177                  | 1.29 (1.02–1.62)            | 3545/21 714 | 108/723                     | 1.21 (0.99–1.46)         | 751/7901                    | 34/810      | 1.68 (1.16–2.43)            |                          |                             |             |                             |
| Definition of subclinical hyperthyroidism                                                                                           |                          |                             |                  |                             |                          |                             |             |                             |                          |                             |             |                             |                          |                             |             |                             |
| Excluding those with missing FT <sub>4</sub> <sup>a</sup>                                                                           | 8129/50 486              | 331/1838                    | 1.29 (1.07–1.56) | 1813/50 456                 | 72/1827                  | 1.36 (1.06–1.75)            | 3545/21 714 | 85/660                      | 1.16 (0.93–1.44)         | 751/7901                    | 19/750      | 1.73 (1.19–2.50)            |                          |                             |             |                             |
| Excluding those with abnormal free or total T <sub>3</sub> <sup>b</sup>                                                             | 8129/50 486              | 353/2045                    | 1.20 (1.01–1.43) | 1813/50 456                 | 75/2036                  | 1.25 (0.98–1.60)            | 3545/21 714 | 99/652                      | 1.19 (0.98–1.46)         | 751/7901                    | 34/763      | 1.64 (1.14–2.35)            |                          |                             |             |                             |
| Thyroid medication use <sup>c</sup>                                                                                                 |                          |                             |                  |                             |                          |                             |             |                             |                          |                             |             |                             |                          |                             |             |                             |
| Including all regardless of thyroid medication use <sup>d</sup>                                                                     | 8198/50 835              | 424/2336                    | 1.22 (1.05–1.42) | 1830/50 803                 | 86/2322                  | 1.26 (1.00–1.58)            | 3585/21 907 | 111/769                     | 1.12 (0.93–1.36)         | 758/8175                    | 35/930      | 1.54 (1.07–2.22)            |                          |                             |             |                             |
| Excluding thyroid medication users at baseline or during follow-up                                                                  | 8079/50 281              | 385/2124                    | 1.25 (1.07–1.47) | 1799/50 252                 | 81/2114                  | 1.32 (1.04–1.67)            | 3515/21 608 | 103/705                     | 1.20 (0.98–1.46)         | 735/7707                    | 30/755      | 1.62 (1.09–2.39)            |                          |                             |             |                             |
| Excluding users of thyroid medication and other medications that could alter thyrotropin and/or FT <sub>4</sub> levels <sup>e</sup> | 8045/50 161              | 376/2096                    | 1.25 (1.07–1.47) | 1792/50 132                 | 79/2086                  | 1.31 (1.03–1.66)            | 3504/21 548 | 103/704                     | 1.20 (0.99–1.47)         | 733/7609                    | 29/734      | 1.62 (1.09–2.41)            |                          |                             |             |                             |
| Outcomes                                                                                                                            |                          |                             |                  |                             |                          |                             |             |                             |                          |                             |             |                             |                          |                             |             |                             |
| Excluding soft CHD outcomes <sup>f</sup>                                                                                            | NA                       | NA                          | NA               | NA                          | NA                       | NA                          | 2934/21 714 | 99/723                      | 1.28 (1.04–1.56)         | NA                          | NA          | NA                          | NA                       | NA                          | NA          | NA                          |
| Only studies with formal adjudication procedures <sup>g</sup>                                                                       | NA                       | NA                          | NA               | 649/7825                    | 25/314                   | 1.50 (1.00–2.27)            | 1627/7838   | 49/314                      | 1.31 (0.98–1.74)         | NA                          | NA          | NA                          | NA                       | NA                          | NA          | NA                          |
| HR calculated until 5 y of follow-up <sup>h</sup>                                                                                   | 2972/50 486              | 184/2188                    | 1.40 (1.13–1.73) | 698/50 456                  | 43/2177                  | 1.61 (1.16–2.22)            | 1585/21 714 | 57/723                      | 1.26 (0.96–1.64)         | 257/6878                    | 13/785      | 1.60 (0.87–2.95)            |                          |                             |             |                             |
| Excluding studies                                                                                                                   |                          |                             |                  |                             |                          |                             |             |                             |                          |                             |             |                             |                          |                             |             |                             |
| Excluding study of cardiac patients <sup>8</sup>                                                                                    | 7882/47 791              | 377/1980                    | 1.26 (1.06–1.51) | 1717/47 761                 | 69/1969                  | 1.18 (0.91–1.53)            | 3392/19 019 | 92/515                      | 1.19 (0.97–1.46)         | NA                          | NA          | NA                          | NA                       | NA                          | NA          | NA                          |
| Excluding study with recent iodine supplementation <sup>9</sup>                                                                     | 7853/47 537              | 255/1254                    | 1.30 (1.10–1.54) | 1776/47 515                 | 61/1252                  | 1.34 (1.03–1.74)            | NA          | NA                          | NA                       | 731/5702                    | 20/118      | 1.81 (1.17–2.79)            |                          |                             |             |                             |
| Excluding study inconsistent with proportional hazard assumption <sup>6</sup>                                                       | 7689/49 471              | 369/2128                    | 1.23 (1.03–1.47) | 1699/49 443                 | 75/2118                  | 1.26 (0.99–1.61)            | NA          | NA                          | NA                       | NA                          | NA          | NA                          | NA                       | NA                          | NA          | NA                          |
| Excluding small study because of potential publication bias <sup>40</sup>                                                           | 8074/49 596              | 383/2098                    | 1.17 (1.03–1.32) | 1804/49 568                 | 81/2088                  | 1.27 (1.00–1.60)            | NA          | NA                          | NA                       | NA                          | NA          | NA                          | NA                       | NA                          | NA          | NA                          |
| Further adjustments of multivariate models                                                                                          |                          |                             |                  |                             |                          |                             |             |                             |                          |                             |             |                             |                          |                             |             |                             |
| Plus lipid-lowering and antihypertensive medications <sup>i</sup>                                                                   | 5696/37 149              | 302/1738                    | 1.20 (1.00–1.45) | 1200/37 122                 | 56/1728                  | 1.26 (0.94–1.69)            | 1962/9493   | 56/337                      | 1.28 (0.98–1.68)         | 747/7850                    | 34/805      | 1.71 (1.18–2.48)            |                          |                             |             |                             |
| Plus BMI <sup>j</sup>                                                                                                               | 7406/48 500              | 354/2069                    | 1.17 (0.99–1.38) | 1635/48 473                 | 70/2059                  | 1.25 (0.96–1.61)            | 3440/20 941 | 102/671                     | 1.23 (1.01–1.50)         | 745/7843                    | 34/803      | 1.68 (1.16–2.43)            |                          |                             |             |                             |

Abbreviations: BMI, body mass index; CHD, coronary heart disease; FT4, free thyroxine; HR, hazard ratio (all age and sex adjusted, except the last two rows); NA, data not applicable; T<sub>3</sub>, triiodothyronine.

<sup>a</sup>A total of 350 participants were excluded in this analysis: CHS (Cardiovascular Health Study), 33; Health ABC (Aging and Body Composition), 29; HUNT Study (Nord-Trøndelag Health Study), 285; SHIP (Study of Health in Pomerania), 2; and Busseon Health Study, 1.

<sup>b</sup>A total of 116 participants with subclinical hyperthyroidism and abnormal free T<sub>3</sub> were excluded in this analysis: Birmingham Study, 4; Leiden 85-Plus Study, 18; Pisa cohort, 53; and SHIP, 41. Twenty-seven participants from the HUNT Study with subclinical hyperthyroidism and abnormal total T<sub>3</sub> level (not measured in other studies) were also excluded.

<sup>c</sup>The numbers of thyroid medication users (ie, thyroxine, antithyroid drugs) during follow-up are given in Table 1.

<sup>d</sup>A total of 497 thyroid medication users (ie, thyroxine, antithyroid drugs) at baseline were added to the overall sample in this sensitivity analysis.

<sup>e</sup>In addition to the 269 thyroid medication users during follow-up, 148 users of other medications that could alter thyrotropin and/or FT4 levels (ie, corticoids, amiodarone, iodine<sup>1,3,10</sup>) were excluded when data were available (CHS, 0; Health ABC Study, 61; SHIP, 87; and Busseon Health Study, 0).

<sup>f</sup>Soft CHD outcomes were defined as hospitalization for angina or revascularization (coronary angioplasty or surgery), and participants with these outcomes were excluded from this analysis, which were available separately in 3 studies.<sup>7,10,38</sup> In contrast, hard outcomes were defined as nonfatal myocardial infarction or CHD death, as defined in the current Framingham risk score.<sup>28</sup>

<sup>g</sup>Formal adjudication procedures were defined as having clear criteria for the outcomes that were reviewed by experts for each potential case, which was possible in 4 studies.<sup>7,8,10,38</sup> For this analysis, CHD adjudication based only on death certificates was not considered as a formal adjudication procedure.

<sup>h</sup>Hazard ratios calculated until 5 years of follow-up were not statistically significantly different from those calculated over complete follow-up data (all  $P > .25$ ). For AF events, the HR until 5 years of follow-up was reduced, likely because of lower power (13 events in subclinical hyperthyroidism instead of 34 over complete follow-up). The HR for AF events became statistically significant with inclusion of later events, and we found a time interaction for AF events ( $P$  value for interaction, .003); rates of AF became higher after 3 years and further increased with additional follow-up data.

<sup>i</sup>All participants of the Birmingham Study and EPIC (European Prospective Investigation of Cancer)—Norfolk Study were excluded from these analyses because of lack of data on lipid-lowering and antihypertensive medications, as well as some participants from other cohorts.

<sup>j</sup>All participants of the Birmingham Study were excluded from these analyses because of lack of data on BMI, as well as some participants from other cohorts.