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

THESE

préparée sous la direction du Professeur Nicolas Rodondi, MER1
à l'Université de Lausanne et à l'Hôpital de l'île, Université de Berne

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

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

Lausanne, le 18 octobre 2012

*pour Le Doyen
de la Faculté de Biologie et de Médecine*



*Madame le Professeur Stephanie Clarke
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Rapport de synthèse

Contexte

L'hyperthyroïdie infra-clinique est une perturbation de la fonction thyroïdienne, définie par une thyrotropine (TSH) basse et des taux normaux de thyroxine libre (T4L) et triiodothyronine (T3). Cette dysfonction affecte de 1% à 5% des adultes de plus de 65 ans, surtout les femmes, et pourrait être associée avec les maladies cardiovasculaires, la fibrillation auriculaire et l'insuffisance cardiaque. Toutefois, les conclusions des différentes études de cohortes sont contradictoires, avec des limites méthodologiques empêchant leur comparaison de manière formelle. L'objet du travail de thèse était d'estimer le risque de mortalité de toute cause, le risque de mortalité de cause cardiovasculaire, le risque d'événements cardiovasculaires et le risque de fibrillation auriculaire associés à l'hyperthyroïdie infra-clinique dans toutes les grandes études de cohorte prospectives disponibles à ce jour.

Méthode et Résultats

Les données individuelles de 52'674 participants provenant de 10 études de cohorte prospectives des Etats-Unis, d'Europe, du Brésil et d'Australie ont été analysées pour évaluer les risques à long-terme de l'hyperthyroïdie infra-clinique. L'euthyroïdie était définie par une TSH entre 0.45 et 4.49 mUI/l et l'hyperthyroïdie infra-clinique par une TSH inférieure à 0.45 mUI/l avec un taux normal de T4L, après exclusion des participants prenant des médicaments pouvant perturber la thyroïde.

Sur les 52'674 participants, 2188 (4.2%) avaient une hyperthyroïdie infra-clinique. Pendant un suivi de plus de 8 ans, 8527 participants sont décédés (dont 1896 de cause cardiovasculaire), 3653 sur 22'437 ont eu un événement cardiovasculaire et 785 sur 8711 ont développé une fibrillation auriculaire. Dans des analyses ajustées pour l'âge et le sexe, l'hyperthyroïdie infra-clinique était associée à une hausse de la mortalité de toute cause (*hazard ratio* [HR] 1.24, intervalle de confiance à 95% [IC] 1.06-1.46), de la mortalité cardiovasculaire (HR 1.29, IC 1.02-1.62), des événements cardiovasculaires (HR 1.21, IC 0.99-1.46) ainsi qu'une hausse de l'incidence de fibrillation auriculaire (HR 1.68, IC 1.16-2.43). Les risques ne différaient pas significativement dans les analyses stratifiées selon l'âge, le sexe ou la présence de maladies cardiovasculaires préexistantes, et étaient similaires après ajustement multiple pour les facteurs de risque cardiovasculaire. Le risque de mortalité cardiovasculaire et de fibrillation auriculaire était plus élevé avec une TSH très basse (< 0.10 UI/l) comparé à une TSH modérément abaissée (0.10-0.44 mUI/l, valeurs *p for trend* ≤ 0.03).

Conclusions et perspectives

L'hyperthyroïdie infra-clinique est associée à un risque augmenté de mortalité de toute cause, de cause cardiovasculaire et de fibrillation auriculaire, avec un risque plus élevé quand la TSH est inférieure à 0.10 mUI/l. Ces résultats sont cohérents avec les dernières recommandations internationales conseillant de considérer un traitement de l'hyperthyroïdie infra-clinique pour les adultes de plus de 65 ans ou les patients avec maladie cardiaque, en particulier si la TSH est inférieure à 0.10 mUI/l. Toutefois, des études cliniques randomisées sont encore nécessaires pour prouver l'efficacité du traitement et déterminer si l'on devrait dépister les problèmes de thyroïde dans la population générale.

Lausanne, le 31 juillet 2012



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Subclinical Hyperthyroidism and the Risk of Coronary Heart Disease and Mortality

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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, $\leq .03$).

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.

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SUBCLINICAL HYPERTHYROIDISM, defined by low thyrotropin level with normal concentrations of free thyroxine (FT₄) and triiodothyronine (T₃),¹⁻⁴ has been associated with several biological effects on cardiovascular system, such as increased heart rate, left ventricular mass, carotid intima-media thickness, and plasma fibrinogen levels.^{3,5} Observational studies

tion.^{13,14} Results from prospective cohort studies are conflicting,^{6,10} and study-level meta-analyses have reached contradictory conclusions, for example, regarding the association between subclinical hyperthyroidism and cardiovascular mortality.¹⁵⁻¹⁷ In fact, interpretation of these studies is hampered by several methodological factors: population heterogeneity, different thyrotropin cutoff levels for

*See Invited Commentary
at end of article*

have reported an association between subclinical hyperthyroidism and coronary heart disease (CHD),⁶⁻⁸ incident atrial fibrillation (AF),⁹⁻¹² and cardiac dysfunc-

See also page 811

subclinical hyperthyroidism definition, different use of covariates, and different CHD definitions.¹⁶ Although no large randomized controlled trials have examined the effects of treating subclinical hyper-

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Group Information:
Participating studies of the Thyroid Studies Collaboration are listed at the end of the article.

thyroidism on clinically relevant outcomes, a consensus statement² and recent guidelines⁴ 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)¹⁸ and allows performance of time-to-event analyses.¹⁹

On the basis of data from the Thyroid Studies Collaboration,²⁰ 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,²⁰ 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 FT₄), 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 FT₄ levels). We performed an additional systematic literature review for articles reporting incident AF events and updated our previous search²⁰ 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 Collaboration²⁰ and included individual demographic characteristics; thyrotropin, FT₄, and total T₃ or free T₃ 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,²⁰ we used a uniform thyrotropin cutoff level for subclinical hyperthyroidism definition, based on an expert consensus meeting of our collaboration²⁰ (International Thyroid Conference, Paris, France, 2010), expert reviews,^{1,21} and previous large cohorts.^{10,22,23} Subclinical hyperthyroidism was defined as a thyrotropin level lower than 0.45 mIU/L with normal FT₄ 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.¹⁻⁴ Data from cohorts using first-generation thyrotropin assays (functional sensitivity, 1-2 mIU/L) were excluded^{9,24,25} because subclinical hyperthyroid-

ism cannot be diagnosed using these methods.²⁶ For FT₄ and total and free T₃, we used study-specific cutoff values because these measurements show greater intermethod variation than thyrotropin assays. For participants with missing values of FT₄ and total or free T₃ (measured in 5 of 10 cohorts [eTable]), we performed sensitivity analyses excluding (1) participants with missing FT₄ values and (2) those with abnormal total or free T₃ levels.^{1-9,21}

Outcomes were total mortality, CHD mortality, CHD events, and incident AF. Stroke and cancer mortality were available for all cohorts except one.²⁷ As in our previous analysis,²⁰ we used homogenous definitions to reduce the heterogeneity in outcomes.^{15,16} Similar to the Framingham risk score,²⁸ 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 events²⁸) or hospitalization for angina or coronary revascularization.¹⁰ 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 criteria¹⁶ 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 model²⁹ as recommended.^{19,30,31} Results were summarized using forest plots (Review Manager 5.1.2, Nordic Cochrane Centre). To assess heterogeneity across studies, we used the I² statistic, which measures the inconsistency across studies attributable to heterogeneity instead of chance alone.³²

Primary analyses were adjusted for age and sex (some traditional cardiovascular risk factors being potential mediators³), 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,³³ complete case analysis was used.

To explore potential sources of heterogeneity, we performed predefined subgroup and sensitivity analyses, as in our previous analysis.²⁰ 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 methods³⁴ to calculate hazard ratios (HRs) and 95% confidence intervals. To calculate age- and sex-adjusted event rates/1000 person-years, we used Poisson models.³⁵ We checked the proportional hazard assumption using graphical methods and the Schoenfeld test.³⁶ For publication bias, we used age- and sex-adjusted funnel plots and the Egger test.³⁷

RESULTS

Among identified reports, 13 prospective cohorts met all inclusion criteria (eFigure). We excluded 3 cohorts^{9,24,25} using first-generation thyrotropin assays,²⁶

Table 1. Baseline Characteristics of Individuals in Included Studies

Source	Description of Study Sample	No. of Participants	Age, Median (Range), y ^a	No. (%)			Follow-up ^d		
				Women	Endogenous Subclinical Hyperthyroidism ^b	Thyroid Medication During Follow-up ^c	Start	Duration, Median (IQR)	Person-years
United States									
Cardiovascular Health Study ¹⁰	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 ³⁸	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 ⁶	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 ²³	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 ²⁷	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 ⁷	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 ⁸	Patients admitted to the cardiology department in Pisa, Italy ⁶	2903	63 (19-92)	927 (31.9)	208 (7.2)	0	2000-2005	2.6 (1.6-3.8)	7966
SHIP ³⁹	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 ²²	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 ⁴⁰	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
Overall		52 674	59 (18-100)	30 828 (58.5)	2188 (4.2)	269 (0.5)	1981-2005	8.8 (7.9-12.4)	501 922

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.

^aParticipants younger than 18 years were excluded.

^bWe 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.

^cData 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.

^dFor all cohorts, we used the maximal follow-up data that were available, which might differ from previous reports for some cohorts.

^ePatients with acute coronary syndrome or severe illness were excluded from the Pisa cohort.

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.^{7,8,10,38} 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 hyperthyroid-

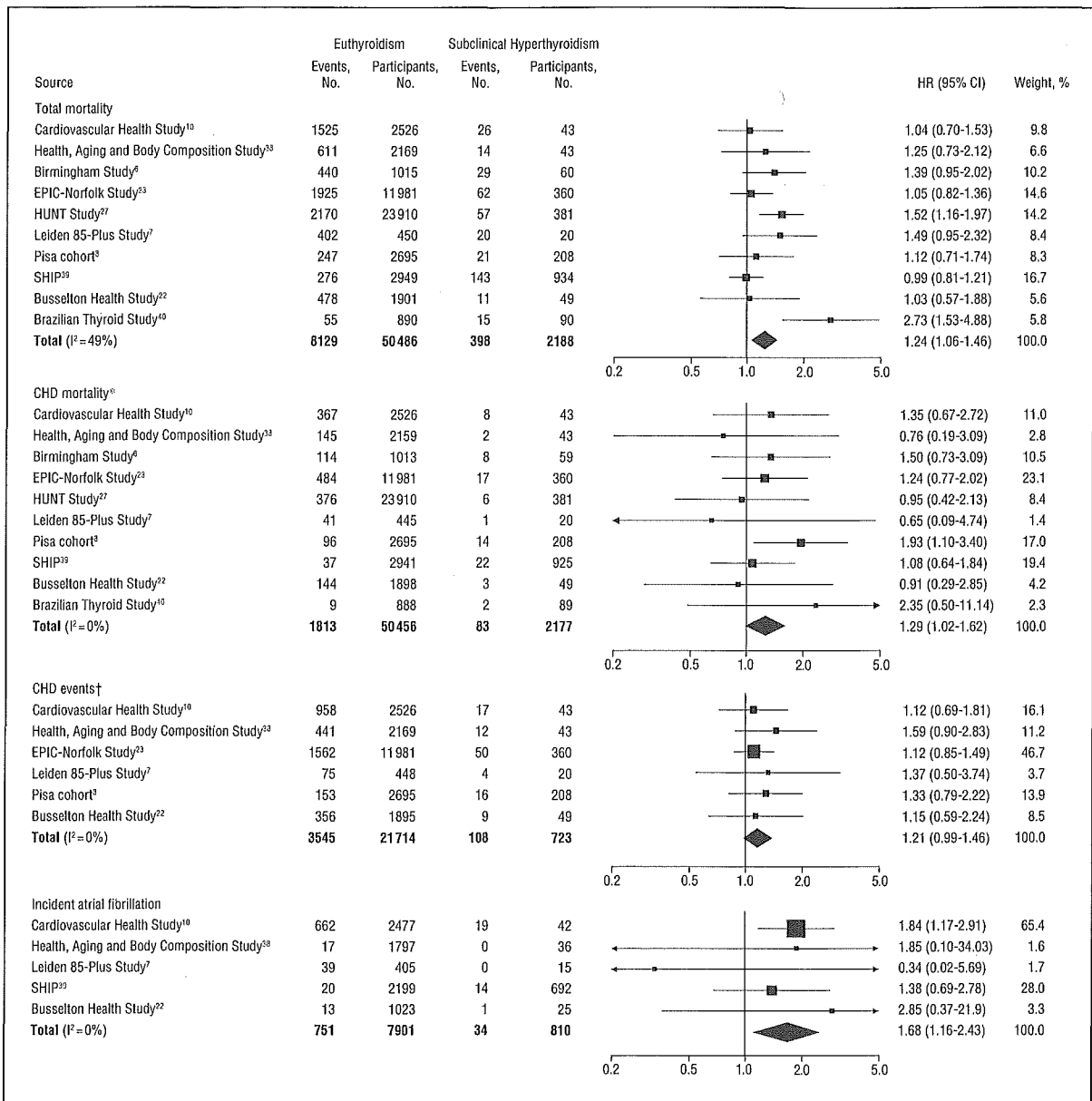


Figure. Total mortality, coronary heart disease (CHD) mortality, CHD events, and atrial fibrillation in endogenous subclinical hyperthyroidism vs euthyroidism. Age and sex-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) are represented by squares or diamonds, those to the right 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,⁶ HUNT (Nord-Trøndelag Health Study),²⁷ SHIP (Study of Health in Pomerania),³⁹ and Brazilian Thyroid Study¹⁰ were not included because follow-up data were only available for death. EPIC indicates European Prospective Investigation of Cancer.

ism 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, $\leq .02$). 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,

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 ^b			
	Events/Participants, No.		HR (95% CI)		Events/Participants, No.		HR (95% CI)	
	Euthyroidism	Subclinical Hyperthyroidism	Age/ Sex-Adjusted	Multivariate Model ^a	Euthyroidism	Subclinical Hyperthyroidism	Age/ Sex-Adjusted	Multivariate Model ^a
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)
P value for interaction			.31	.31			.35	.30
Age, y ^c								
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 ^d	64/729 ^d	1.29 (0.87-1.91)	1.24 (0.85-1.80)	236/17 885 ^d	7/728 ^d	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 ^d	8/73 ^d	1.16 (0.58-2.30)	0.79 (0.34-1.84)
P value for trend			.45	.18			.05	.06
Race ^e								
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)
P 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)
P value for trend			.19	.77			.02	.16
Preexisting CVD ^f								
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)
P value for interaction			.93	.83			.44	.59
			CHD Events ^g				Incident AF ^h	
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)
P value for interaction			.25	.18			.90	.61
Age, y ^c								
18-49	114/4112	6/122	2.49 (0.46-13.44)	2.41 (0.43-13.46)	2/1261 ^d	1/269 ^d	1.48 (0.13-16.90)	1.19 (0.06-23.40)
50-64	816/7344 ^d	18/261 ^d	0.78 (0.49-1.26)	0.81 (0.50-1.29)	15/966 ^d	5/249 ^d	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 ^d	5/24 ^d	1.35 (0.42-4.35)	1.11 (0.45-2.70)
P value for trend			.45	.50			.92	.93
Race ^e								
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
P 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)
P value for trend			.74	.61			.03	.06
Preexisting CVD ^g								
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 ^d	7/64 ^d	1.44 (0.46-4.58) ^d	2.05 (0.98-4.32) ^d
P 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.

^aAdjusted 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.

^bForty-one participants were excluded from the analyses of CHD mortality because of missing cause of death.

^cThese HRs were adjusted for sex and age as a continuous variable to avoid residual confounding within age strata.

^dSome strata from specific studies were excluded when there was no event in a subgroup.

^eData on race were not available for the Birmingham study (n = 1075). The Asian group was only from the Brazilian (of Japanese descent) Thyroid Study.

^fData 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 Busselton Health Study. For analysis of CHD events, 32 participants of EPIC-Norfolk Study and Busselton Health Study were excluded for the same reason.

^gThe 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.

^hParticipants 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 Busselton 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		
	Events/Participants, No.			Events/Participants, No.		
	Euthyroidism	Subclinical Hyperthyroidism	HR (95% CI)	Euthyroidism	Subclinical Hyperthyroidism	HR (95% CI)
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)
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)
Definition of subclinical hyperthyroidism						
Excluding those with missing FT ₄ ^a	8129/50 486	331/1838	1.29 (1.07-1.56)	1813/50 456	72/1827	1.36 (1.06-1.75)
Excluding those with abnormal free or total T ₃ ^b	8129/50 486	353/2045	1.20 (1.01-1.43)	1813/50 456	75/2036	1.25 (0.98-1.60)
Thyroid medication use ^c						
Including all regardless of thyroid medication use ^d	8198/50 835	424/2336	1.22 (1.05-1.42)	1830/50 803	86/2322	1.26 (1.00-1.58)
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)
Excluding users of thyroid medication and other medications that could alter thyrotropin and/or FT ₄ levels ^e	8045/50 161	376/2096	1.25 (1.07-1.47)	1792/50 132	79/2086	1.31 (1.03-1.66)
Outcomes						
Excluding soft CHD outcomes ^f	NA	NA	NA	NA	NA	NA
Only studies with formal adjudication procedures ^g	NA	NA	NA	649/7825	25/314	1.50 (1.00-2.27)
HR calculated until 5 y of follow-up ^h	2972/50 486	184/2188	1.40 (1.13-1.73)	698/50 456	43/2177	1.61 (1.16-2.22)
Excluding studies						
Excluding study of cardiac patients ⁱ	7882/47 791	377/1980	1.26 (1.06-1.51)	1717/47 761	69/1969	1.18 (0.91-1.53)
Excluding study with recent iodine supplementation ³⁹	7853/47 537	255/1254	1.30 (1.10-1.54)	1776/47 515	61/1252	1.34 (1.03-1.74)
Excluding study inconsistent with proportional hazard assumption ⁹	7689/49 471	369/2128	1.23 (1.03-1.47)	1699/49 443	75/2118	1.26 (0.99-1.61)
Excluding small study because of potential publication bias ⁴⁰	8074/49 596	383/2098	1.17 (1.03-1.32)	1804/49 568	81/2088	1.27 (1.00-1.60)
Further adjustments of multivariate models						
Plus lipid-lowering and antihypertensive medications ¹	5696/37 149	302/1738	1.20 (1.00-1.45)	1200/37 122	56/1728	1.26 (0.94-1.69)
Plus BMI ¹	7406/48 500	354/2069	1.17 (0.99-1.38)	1635/48 473	70/2059	1.25 (0.96-1.61)

(continued)

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, $\leq .03$ 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.⁴⁰ 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.^{7,8,13,38} Risks of total mortality, CHD mortality and incident AF increased slightly after excluding a study with previous iodine supplementation.³⁹ 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 Study⁶ (*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 Study⁴⁰ 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, $\leq .03$). 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

Table 3. Sensitivity Analyses of the Association Between Subclinical Hyperthyroidism and the Risk of Total Mortality, CHD Mortality, CHD Events, and Atrial Fibrillation (continued)

Variable	CHD Events			Incident AF		
	Events/Participants, No.			Events/Participants, No.		
	Euthyroidism	Subclinical Hyperthyroidism	HR (95% CI)	Euthyroidism	Subclinical Hyperthyroidism	HR (95% CI)
All eligible studies						
Random-effects model	3545/21 714	108/723	1.21 (0.99-1.46)	751/7901	34/810	1.68 (1.16-2.43)
Fixed-effects model	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 ₄ ^a	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 ₃ ^b	3545/21 714	99/652	1.19 (0.98-1.46)	751/7901	34/763	1.64 (1.14-2.35)
Thyroid medication use ^c						
Including all regardless of thyroid medication use ^d	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	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 ₄ levels ^e	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 ^f	2934/21 714	99/723	1.28 (1.04-1.56)	NA	NA	NA
Only studies with formal adjudication procedures ^g	1627/7838	49/314	1.31 (0.98-1.74)	NA	NA	NA
HR calculated until 5 y of follow-up ^h	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 ^g	3392/19 019	92/515	1.19 (0.97-1.46)	NA	NA	NA
Excluding study with recent iodine supplementation ³⁹	NA	NA	NA	731/5702	20/118	1.81 (1.17-2.79)
Excluding study inconsistent with proportional hazard assumption ^g	NA	NA	NA	NA	NA	NA
Excluding small study because of potential publication bias ⁴⁰	NA	NA	NA	NA	NA	NA
Further adjustments of multivariate models						
Plus lipid-lowering and antihypertensive medications ⁱ	1962/9493	56/337	1.28 (0.98-1.68)	747/7850	34/805	1.71 (1.18-2.48)
Plus BMI ^j	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 2 rows); NA, data not applicable; T₃, triiodothyronine.

^aA 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 Busseton Health Study, 1.

^bA total of 116 participants with subclinical hyperthyroidism and abnormal free T₃ 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 T₃ level (not measured in other studies) were also excluded.

^cThe numbers of thyroid medication users (ie, thyroxine, antithyroid drugs) during follow-up are given in Table 1.

^dA total of 497 thyroid medication users (ie, thyroxine, antithyroid drugs) at baseline were added to the overall sample in this sensitivity analysis.

^eIn 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^{3,8,10}) were excluded when data were available (CHS, 0; Health ABC Study, 61; SHIP, 87; and Busseton Health Study, 0).

^fSoft 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.^{7,10,38} In contrast, hard outcomes were defined as nonfatal myocardial infarction or CHD death, as defined in the current Framingham risk score.²⁸

^gFormal 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.^{7,8,10,38} For this analysis, CHD adjudication based only on death certificates was not considered as a formal adjudication procedure.

^hHazard 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.

ⁱAll 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.

^jAll 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.

hyperthyroidism and cardiovascular mortality.¹⁵⁻¹⁷ Our results, based on individual participant data, demonstrate that there is indeed an increased risk of total and CHD mortality associated with subclinical hyperthyroidism,^{15,16} 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 analysis¹⁸ and they pooled individual studies using varying thyrotropin cutoff levels, outcome definitions, and confounding factors for adjustment.^{15,16} Only a few individual studies reported stratified

risks according to thyrotropin levels. Our results are consistent with those recently reported by Vadiveloo et al,⁴¹ 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.^{9,10} Sawin et al⁹ 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.²⁶ Cappola et al¹⁰ 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 al¹¹ 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^{1,3} or cardiac arrhythmia.^{3,42} 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.⁴³ Sensitivity analyses (1) excluding a small study⁴⁰ 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)¹⁸ and allows performance of time-to-event analyses and use of standardized definitions of predictors, outcomes, and adjustment for confounding factors.¹⁹ 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.⁴⁰ 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.^{10,23,27,38} Third, subclinical hyperthyroidism was defined as a thyrotropin level lower than 0.45 mIU/L and normal FT₄ levels, since T₃ was not measured in all included cohorts; sensitivity analyses excluding participants with abnormal total or free T₃ 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.⁴⁴ 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.⁴⁵ 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 FT₄ 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.¹ Eighth, 4 of 6 studies^{7,8,10,38} 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 guidelines⁴ 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.⁴ 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 hy-

pothyroidism. If conducted, such a trial should examine prevention of AF and surrogate outcome measures, such as carotid intima-media thickness.⁴⁶

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Online-Only Material: The eAppendix, eTable, and eFigure are available at <http://www.archinternmed.com>. Visit <http://www.archinternmed.com> to listen to an author podcast about this article.

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