ORIGINAL INVESTIGATION

Subclinical Hyperthyroidism and the Risk of Coronary Heart Disease and Mortality

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Tinh-Hai Collet, MD; Jacobijn Gussekloo, MD, PhD; Douglas C. Bauer, MD; Wendy P. J. den Elzen, PhD; Anne R. Cappola, MD, ScM; Philippe Balmer, BSc; Giorgio Iervasi, MD; Bjørn O. Åsvold, MD, PhD; José A. Sgarbi, MD; Henry Völzke, MD; Bariş Gencer, MD; Rui M. B. Maciel, MD; Sabrina Molinaro, PhD; Alexandra Bremner, PhD; Robert N. Luben, PhD; Patrick Maisonneuve, Ing; Jacques Cornuz, MD, MPH; Anne B. Newman, MD, MPH; Kay-Tee Khaw, MD; Rudi G. J. Westendorp, MD, PhD; Jayne A. Franklyn, MD, PhD, FRCP, FMedSci; Eric Vittinghoff, PhD; John P. Walsh, MBBS, FRACP, PhD; Nicolas Rodondi, MD, MAS; for the Thyroid Studies Collaboration

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.

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Subclinical hyperthyroidism, defined by low thyrotropin level with normal concentrations of free thyroxine (FT_4) and triiodothyronine (T_3),[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 have reported an association between subclinical hyperthyroidism and coronary heart disease (CHD),[6-8] incident atrial fibrillation (AF),[9-12] and cardiac dysfunction.[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 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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Author Affiliations are listed at the end of this article.
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thyroidism on clinically relevant outcomes, a consensus statement[2] and recent guidelines[4] 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 FT_4), 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_4 levels). We performed an additional systematic literature review for articles reporting incident AF events and updated our previous search[20] 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[20] and included individual demographic characteristics; thyrotropin, FT_4, and total T_3 or free T_3 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 collaboration[20] (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 FT_4 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 hyperthyroidism cannot be diagnosed using these methods.[26] For FT_4 and total and free T_3, we used study-specific cutoff values because these measurements show greater intermethod variation than thyrotropin assays. For participants with missing values of FT_4 and total or free T_3 (measured in 5 of 10 cohorts [eTable]), we performed sensitivity analyses excluding (1) participants with missing FT_4 values and (2) those with abnormal total or free T_3 levels.[1-4,21]

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 events[28]) 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 criteria[16] 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[29] 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 I^2 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 mediators[3]), 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 methods[34] 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]

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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[e]	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.

[a] Participants younger than 18 years were excluded.

[b] 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.

[c] 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.

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

[e] Patients 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-

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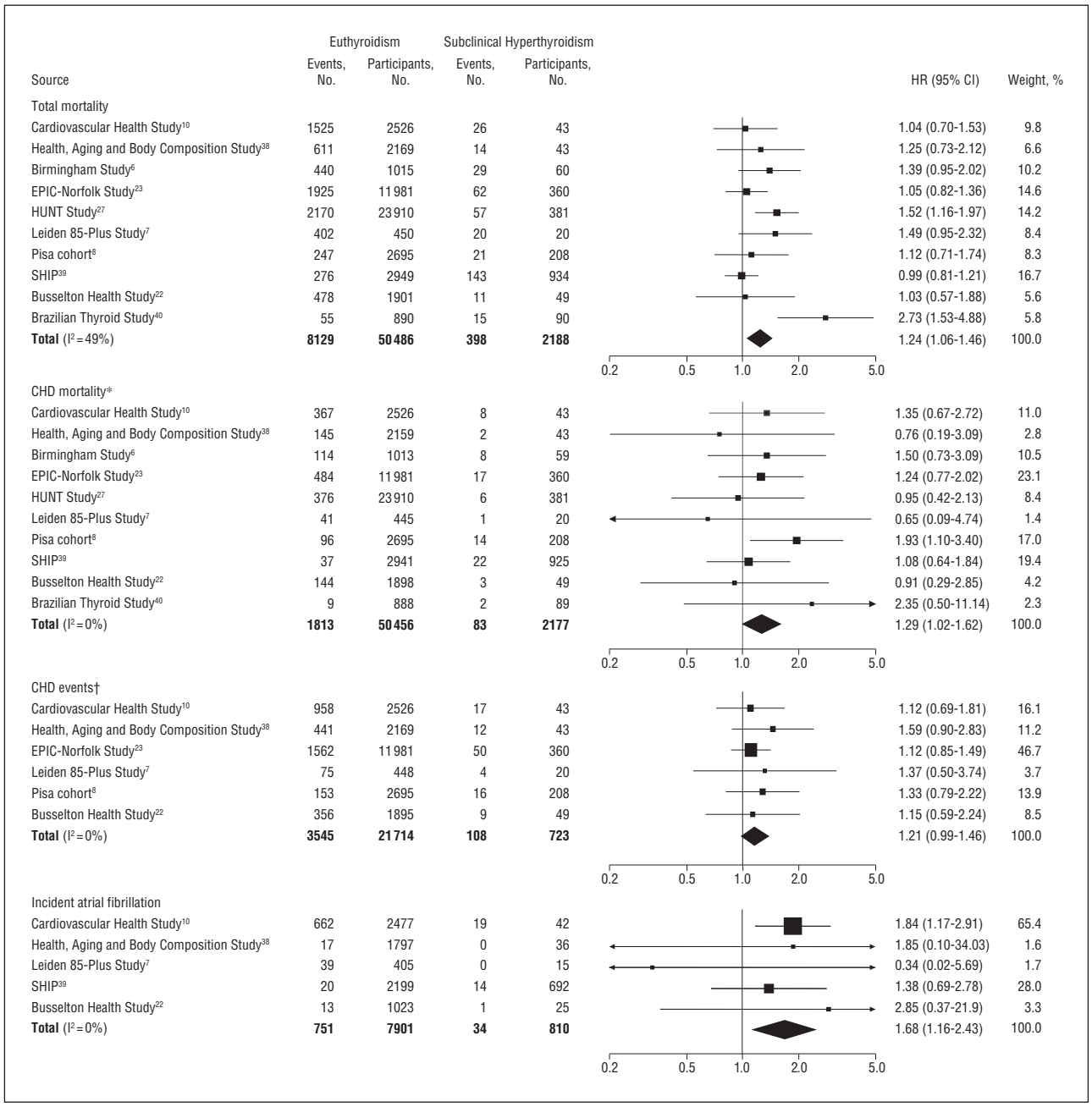

Figure. Total mortality, coronary heart disease (CHD) mortality, CHD events, and atrial fibrillation in endogenous subclinical hyperthyroidism vs euthyroidism. Age and sex-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) are represented by squares or diamonds, those to the right 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,[6] HUNT (Nord-Trøndelag Health Study),[27] SHIP (Study of Health in Pomerania),[39] and Brazilian Thyroid Study[40] 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, ≤.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,

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

	Total Mortality				CHD Mortality[b]			
	Events/Participants, No.		HR (95% CI)		Events/Participants, No.		HR (95% CI)	
Variable	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.

[a] 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.

[b] Forty-one participants were excluded from the analyses of CHD mortality because of missing cause of death.

[c] These HRs were adjusted for sex and age as a continuous variable to avoid residual confounding within age strata.

[d] Some strata from specific studies were excluded when there was no event in a subgroup.

[e] 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.

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

[g] 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.

[h] 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 Busselton Health Study, 11 and 891, respectively.

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

	Total Mortality			CHD Mortality		
	Events/Participants, No.			Events/Participants, No.		
Variable	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[8]	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[6]	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[i]	5696/37 149	302/1738	1.20 (1.00-1.45)	1200/37 122	56/1728	1.26 (0.94-1.69)
Plus BMI[j]	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, ≤.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 Study[6] ($P = .009$), 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[40] 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

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

	CHD Events			Incident AF		
	Events/Participants, No.			Events/Participants, No.		
Variable	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[8]	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[6]	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; FT_4, free thyroxine; HR, hazard ratio (all age and sex adjusted, except the last 2 rows); NA, data not applicable; T_3, triiodothyronine.

[a] 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 Busselton Health Study, 1.

[b] A total of 116 participants with subclinical hyperthyroidism and abnormal free T_3 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_3 level (not measured in other studies) were also excluded.

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

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

[e] In addition to the 269 thyroid medication users during follow-up, 148 users of other medications that could alter thyrotropin and/or FT_4 levels (ie, corticoids, amiodarone, iodine[1,3,10]) were excluded when data were available (CHS, 0; Health ABC Study, 61; SHIP, 87; and Busselton Health Study, 0).

[f] 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.[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]

[g] 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.[7,8,10,38] For this analysis, CHD adjudication based only on death certificates was not considered as a formal adjudication procedure.

[h] 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.

[i] 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.

[j] 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.

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 analysis[18] 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

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hyperthyroidism.[9,10] Sawin et al[9] 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 al[10] 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[41] 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 study[40] 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 FT_4 levels, since T_3 was not measured in all included cohorts; sensitivity analyses excluding participants with abnormal total or free T_3 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 FT_4 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 guidelines[4] 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-

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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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Author Affiliations: Department of Ambulatory Care and Community Medicine, University of Lausanne, Lausanne, Switzerland (Drs Collet, Gencer, and Cornuz and Mr Balmer); Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, the Netherlands (Drs Gussekloo and den Elzen); Departments of Medicine (Dr Bauer) and Epidemiology and Biostatistics (Drs Bauer and Vittinghoff), University of California, San Francisco; Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia (Dr Cappola); National Council Research Institute of Clinical Physiology/Tuscany Region G. Monasterio Foundation, Pisa, Italy (Drs Iervasi and Molinaro); Department of Public Health, Norwegian University of Science and Technology, Trondheim, Norway (Dr Åsvold); Division of Endocrinology, Department of Medicine, Federal University of São Paulo, Brazil (Drs Sgarbi and Maciel); Division of Endocrinology, Faculdade de Medicina de Marília, Marília, Brazil (Dr Sgarbi); Institute for Community Medicine, Clinical-Epidemiological Research, University of Greifswald, Greifswald, Germany (Dr Völzke); Schools of Population Health (Dr Bremner) and Medicine and Pharmacology (Dr Walsh), The University of Western Australia, Crawley, Australia; Department of Public Health and Primary Care, University of Cambridge, Cambridge, England (Drs Luben and Khaw); Division of Epidemiology and Biostatistics, European Institute of Oncology, Milano, Italy (Dr Maisonneuve); Department of Epidemiology, University of Pittsburgh, Pittsburgh, Pennsylvania (Dr Newman); Department of Gerontology and Geriatrics, Leiden University Medical Center, and Netherlands Consortium for Healthy Ageing, Leiden (Dr Westendorp); School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham, Birmingham, England (Dr Franklyn); Department of Endocrinology & Diabetes, Sir Charles Gairdner Hospital, Nedlands, Australia (Dr Walsh); and Department of General Internal Medicine, Inselspital, University of Bern, Bern, Switzerland (Dr Rodondi).
Correspondence: Nicolas Rodondi, MD, MAS, Department of General Internal Medicine, Inselspital, University of Bern, 3010 Bern, Switzerland (Nicolas.Rodondi@insel.ch).
Author Contributions: Drs Collet and Rodondi had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Gussekloo, Newman, Westendorp, Franklyn, and Rodondi. *Acquisition of data:* Gussekloo, den Elzen, Iervasi, Åsvold, Sgarbi, Völzke, Gencer, Maciel, Molinaro, Luben, Newman, Khaw, Westendorp, Franklyn, Walsh, and Rodondi. *Analysis and interpretation of data:* Collet, Gussekloo, Bauer, den Elzen, Cappola, Balmer, Iervasi, Åsvold, Sgarbi, Völzke, Gencer, Maciel, Bremner, Maisonneuve, Cornuz, Westendorp, Franklyn, Vittinghoff, and Rodondi. *Drafting of the manuscript:* Collet, Balmer, Maciel, Westendorp, and Franklyn. *Critical revision of the manuscript for important intellectual content:* Collet, Gussekloo, Bauer, Cappola, Balmer, Iervasi, Åsvold, Sgarbi, Völzke, Gencer, Molinaro, Bremner, Luben, Maisonneuve, Cornuz, Newman, Khaw, Westendorp, Franklyn, Vittinghoff, Walsh, and Rodondi. *Statistical analysis:* Collet, Gussekloo, Balmer, Gencer, Franklyn, Vittinghoff, and Rodondi. *Obtained funding:* Sgarbi, Völzke, Maciel, Newman, Khaw, Westendorp, Walsh, and Rodondi. *Administrative, technical, and material support:* Collet, den Elzen, Gencer, Maciel, Luben, Newman, Khaw, Franklyn, and Rodondi. *Study supervision:* Gussekloo, Iervasi, Molinaro, Westendorp, and Rodondi. Dr Vittinghoff reviewed the statistical analyses of the manuscript.
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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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INVITED COMMENTARY

What Is the Clinical Importance of Subclinical Hyperthyroidism?

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Subclinical hyperthyroidism is defined as a patient having normal free thyroxine (FT_4) and total triiodothyronine (T_3) levels in conjunction with a thyrotropin (TSH) level persistently below the normal range in the absence of factors known to suppress TSH. Factors that may alter TSH value and thyroid function test results include medications such as corticosteroids and dopamine and clinical conditions to include hypothalamic or pituitary hypofunction and nonthyroid illness.[1,2] Nonthyroid illness is a general term that applies to a wide variety of patients who have systemic illness that can result in altered thyroid function test results. In general, the diagnosis of subclinical hyperthyroidism is made in ambulatory outpatients who are not taking medications known to affect thyroid function. The incidence of subclinical hyperthyroidism is approximately 1%.[3] The most common causes of endogenous subclinical hyperthyroidism include Graves disease (usually younger patients), multinodular goiter (typically older patients), and solitary autonomous nodules. The discrimination between endogenous hyperthyroidism from exogenous hyperthyroidism is important, since exogenous hyperthyroidism can usually be treated by modulation of the levothyroxine dose. Although the study by Collet et al[4] focuses on cardiovascular effects, subclinical hyperthyroidism is also associated with an increased risk of osteopenia and/or osteoporosis, especially in older women, which may improve following treatment of the hyperthyroidism.[5] It is controversial whether cognitive function is altered by the presence of subclinical hyperthyroidism.

Collet et al[4] analyzed previously published prospective cohort studies to determine the association between total and coronary heart disease (CHD) mortality, CHD events, and atrial fibrillation. Subclinical hyperthyroidism was defined as a normal serum FT_4 concentration in conjunction with a serum TSH value less than 0.45 mIU/L. Their major conclusion was that subclinical hyperthyroidism was associated with increased total mortality, CHD mortality, and atrial fibrillation, irrespective of age, sex, or preexisting cardiovascular disease. There was a trend toward more events if the TSH value was lower than 0.1 mIU/L. Stroke incidence and cancer mortality was not associated with subclinical hyperthyroidism.

These conclusions confirm observational studies, but there has been discordance with regard to CHD events between prospective cohort studies and meta-analyses.[6-8] The study by Collet et al[4] was well performed and executed by experienced authors. The study excluded subjects taking medications known to affect thyroid function test results, patients with elevated FT_4 and decreased TSH values, and studies using insensitive first-generation TSH assays. However, there are potential limitations of the current study. The studies analyzed generally did not have rigorous independent evaluation of cardiovascular events and the results depend on accurate data collection in the original studies. Second-generation assays may not be sufficiently sensitive to discern small differences in TSH values especially below the lower limit of the normal range. Total or free T_3 levels were not regularly measured, and it is possible some of these patients had "T_3 toxicosis" (ie, hyperthyroidism) and thyroid function was only measured at baseline.

Given the potential adverse effects of subclinical hyperthyroidism, what clinical advice can be given when evaluating a patient with decreased serum TSH and normal FT_4 values? It is important to perform a detailed history and physical examination and obtain relevant clinical and radiologic (eg, thyroid ultrasound examination, radioactive iodine uptake and scan, bone mineral density, electrocardiography) and laboratory studies (eg, complete blood cell count with differential, comprehensive metabolic profile FT_4, free T_3/total T_3, TSH, and in some instances thyroid antibodies and thyroid-stimulating immunoglobulins) to assess the possible causes of subclinical hyperthyroidism and its potential adverse effects. Prior to treating subclinical hyperthyroidism, guidelines recommend repeating thyroid function tests at 3 and 6 months to confirm stability.[2] Subclinical hyperthyroidism may not be persistent, and TSH level may return to normal or, alternatively, may rarely progress to overt hy-

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