SUBCLINICAL HYPOTHYROIDISM AND THE RISK OF CORONARY HEART DISEASE AND MORTALITY: AN INDIVIDUAL PARTICIPANT DATA ANALYSIS FROM NINE PROSPECTIVE COHORT STUDIES

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Subclinical Hypothyroidism and the Risk of Coronary Heart Disease and Mortality

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Context Data regarding the association between subclinical hypothyroidism and cardiovascular disease outcomes are conflicting among large prospective cohort studies. This might reflect differences in participants' age, sex, thyroid-stimulating hormone (TSH) levels, or preexisting cardiovascular disease.

Objective To assess the risks of coronary heart disease (CHD) and total mortality for adults with subclinical hypothyroidism.

Data Sources and Study Selection The databases of MEDLINE and EMBASE (1950 to May 31, 2010) were searched without language restrictions for prospective cohort studies with baseline thyroid function and subsequent CHD events, CHD mortality, and total mortality. The reference lists of retrieved articles also were searched.

Data Extraction Individual data on 55 287 participants with 542 494 person-years of follow-up between 1972 and 2007 were supplied from 11 prospective cohorts in the United States, Europe, Australia, Brazil, and Japan. The risk of CHD events was examined in 25 977 participants from 7 cohorts with available data. Euthyroidism was defined as a TSH level of 0.50 to 4.49 mIU/L. Subclinical hypothyroidism was defined as a TSH level of 4.5 to 19.9 mIU/L with normal thyroxine concentrations.

Results Among 55 287 adults, 3450 had subclinical hypothyroidism (6.2%) and 51 837 had euthyroidism. During follow-up, 9664 participants died (2168 of CHD), and 4470 participants had CHD events (among 7 studies). The risk of CHD events and CHD mortality increased with higher TSH concentrations. In age- and sex-adjusted analyses, the hazard ratio (HR) for CHD events was 1.00 (95% confidence interval [CI], 0.86-1.18) for a TSH level of 4.5 to 6.9 mIU/L (20.3 vs 20.3/1000 person-years for participants with euthyroidism), 1.17 (95% CI, 0.96-1.43) for a TSH level of 7.0 to 9.9 mIU/L (23.8/1000 person-years), and 1.89 (95% CI, 1.28-2.80) for a TSH level of 10 to 19.9 mIU/L (n=70 events/235; 38.4/1000 person-years; $P<.001$ for trend). The corresponding HRs for CHD mortality were 1.09 (95% CI, 0.91-1.30; 5.3 vs 4.9/1000 person-years for participants with euthyroidism), 1.42 (95% CI, 1.03-1.95; 6.9/1000 person-years), and 1.58 (95% CI, 1.10-2.27, n=28 deaths/333; 7.7/1000 person-years; $P=.005$ for trend). Total mortality was not increased among participants with subclinical hypothyroidism. Results were similar after further adjustment for traditional cardiovascular risk factors. Risks did not significantly differ by age, sex, or preexisting cardiovascular disease.

Conclusions Subclinical hypothyroidism is associated with an increased risk of CHD events and CHD mortality in those with higher TSH levels, particularly in those with a TSH concentration of 10 mIU/L or greater.

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CONTROVERSY PERSISTS ON THE indications for screening and threshold levels of thyroid-stimulating hormone (TSH) for treatment of subclinical hypothyroidism,[1-3] defined as elevated serum TSH levels with normal thyroxine (T_4) concentrations. Because subclinical hypothyroidism has been associated with hypercholesterolemia[4] and atherosclerosis,[5] screening and treatment have been advocated to prevent cardiovascular disease.[3] However, data on the associations with coronary heart disease (CHD) events and mortality are conflicting among several large prospective cohorts.[6-9] Three recent study-level meta-analyses[10-12] found modestly increased risks for CHD and mortality, but with heterogeneity among individual studies that used different TSH cutoffs, dif-

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ferent confounding factors for adjustment, and varying CHD definitions.[10] Part of the heterogeneity might also be related to differences in participants' age, sex, or severity of subclinical hypothyroidism (as measured by TSH level).[4] One cohort study suggested particularly high risk in participants with subclinical hypothyroidism and preexisting cardiovascular disease.[8]

Analysis of individual participant data from large cohort studies may reconcile these conflicting data and define the influence of age, TSH levels, and preexisting cardiovascular disease. 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)[13] and allows performance of time-to-event analyses.[14]

To clarify the cardiovascular risk of subclinical hypothyroidism, we formed the Thyroid Studies Collaboration and conducted an individual participant data analysis of subclinical hypothyroidism and CHD outcomes.

METHODS

Identification of potential studies was based on protocols developed for our study-level meta-analysis of prospective cohort studies.[10] Briefly, we conducted a systematic literature search of articles in all languages on the association between subclinical thyroid dysfunction and CHD or mortality (cardiovascular and total) published from 1950 to May 31, 2010, in the MEDLINE and EMBASE databases and searched bibliographies of key articles (details are available in the eMethods at http://www.jama.com). To maximize the quality and comparability of the studies, we formulated general inclusion criteria a priori. We included only full-text, published longitudinal cohort studies that (1) measured thyroid function with both serum TSH level and thyroxine (T_4) level at baseline in adults, (2) followed up participants systematically over time, (3) assessed CHD events and/or mortality, and (4) had a comparison group with euthyroidism. We excluded studies that only examined persons taking antithyroid medications, thyroxine replacement or amiodarone, or with overt hypothyroidism (defined as low T_4 and elevated TSH concentrations). Possible studies for inclusion were independently assessed for suitability by 2 of the authors (N.R., J.G.) and any disagreement was resolved by discussion with a third author (D.C.B). The agreement between the 2 reviewers was 99.9% for the first screen (titles and abstracts, $\kappa = 0.98$) and 100% for the full-text screen ($\kappa = 1.00$).

Investigators from each eligible study were invited to join the Thyroid Studies Collaboration. We collected detailed information about prespecified outcomes and potential confounding variables for each participant. Requested data included individual demographic characteristics, baseline thyroid function (TSH and T_4 levels), baseline cardiovascular risk factors (eg, low- and high-density lipoprotein cholesterol level, diabetes, blood pressure, cigarette smoking), prevalent cardiovascular disease, medication use at baseline (thyroid medication, lipid-lowering and antihypertensive drugs), and outcome data.

To maximize the comparability of the studies, we used a common definition of subclinical hypothyroidism. Based on expert reviews[1,2] and definitions used in the Cardiovascular Health Study,[6,15] we defined subclinical hypothyroidism as a serum TSH level of 4.5 mIU/L or greater to less than 20 mIU/L, with a normal T_4 concentration; and euthyroidism was defined as a serum TSH level of 0.5 mIU/L or greater and less than 4.5 mIU/L. Because the Whickham Survey used a first-generation TSH radioimmunoassay, which gives higher measured TSH values than current assays,[16] a TSH range of 6.0 mIU/L or greater to less than 21.5 mIU/L was used for this individual participant data analyses, as in the original and recent analysis of this study.[17,18] In that study, a serum TSH level of 6.0 mIU/L corresponded to the 97.5th percentile of the group with negative thyroid antibodies,[18] which is close to the modern level of 4.5 mIU/L for the current generation of assays. For T_4 level, we used site- and method-dependent specific cutoffs (eTable at http://www.jama.com) because T_4 measurements show greater intermethod variation than do sensitive TSH assays. The Whickham Survey measured total T_4 level.[18] Participants with abnormal T_4 values, results suggestive of nonthyroidal illness (low TSH and FT_4 levels) or low TSH level (<0.5 mIU/L) were excluded (n = 3023). Some studies had participants with missing T_4 values (eTable); we considered participants with a TSH level of 4.5 mIU/L to 19.9 mIU/L and a missing T_4 level as having subclinical hypothyroidism because most adults with this degree of TSH elevation have subclinical and not overt hypothyroidism.[19] We performed a sensitivity analysis excluding those with a missing T_4 level.

Outcome measures were CHD events, CHD mortality, and total mortality. To limit outcome heterogeneity observed with previous study-level meta-analyses,[10-12] we used more homogeneous outcome definitions. Similar to the current Framingham risk score,[20] we limited cardiovascular mortality to CHD mortality or sudden death (eTable). A CHD event was defined as nonfatal myocardial infarction or CHD death (equivalent to hard events in the Framingham risk score[20]) and hospitalization for angina or coronary revascularization (coronary artery bypass grafting or angioplasty).[6] We performed a sensitivity analysis with hard events only.

Using previously described criteria[10] and new information from study authors, we systematically evaluated the following key indicators of study quality[13]: methods of outcome adjudication and ascertainment, accounting for confounders, and completeness of follow-up ascertainment. Two reviewers (N.R., J.G.) rated all studies for quality.

We used separate Cox proportional hazard models to assess the associations of subclinical hypothyroidism with CHD events and mortality for each cohort (SAS version 9.2, SAS Institute Inc, Cary, North Carolina). Pooled estimates for each outcome were calculated using random-effects models, based

on the variance model according to DerSimonian and Laird,[21] as recommended[14,22] and published in recent 2-stage individual participant data analyses.[23] Results were summarized using forest plots (Review Manager version 5.0.24, Nordic Cochrane Centre, Copenhagen, Denmark). The research authors of 1 study with 14 CHD outcomes[5,10] declined to participate; as recommended,[24] we included the published summary estimate from that study in the random-effects models in a sensitivity analysis. To assess heterogeneity across studies, we used the I^2 statistic, which describes the total variation across studies attributable to heterogeneity rather than chance (I^2>50% indicating at least moderate statistical heterogeneity).[25]

Primary analyses were adjusted for age and sex, and then for traditional cardiovascular risk factors (systolic blood pressure, smoking, total cholesterol, diabetes) that were available in all cohorts (except for the Birmingham Study,[26] which was excluded from this analysis). We considered the age- and sex-adjusted model as the primary analysis because some traditional risk factors are potential mediators of the relationship between subclinical hypothyroidism and CHD.[4]

To explore sources of heterogeneity, we performed several predefined subgroup and sensitivity analyses. We conducted stratified analyses by age, sex, race, TSH concentrations, and preexisting cardiovascular disease. Based on expert reviews[1,2] and previous studies,[7,15] subclinical hypothyroidism was stratified according to the following TSH concentration categories: 4.5-6.9 mIU/L (mild elevation), 7.0-9.9 mIU/L (moderate elevation), and 10.0-19.9 mIU/L (marked elevation). In the study-specific analyses stratified by age or TSH level, some strata had participants without either CHD deaths or CHD events (for 1 study[27]). For these study-specific analyses, we used penalized likelihood methods[28] to obtain hazard ratios (HRs) and confidence intervals (CIs). As done in previous studies,[7,27,29] after including all participants in the primary analyses, we performed sensitivity analyses excluding participants who had thyroid hormone use at baseline and during follow-up. To calculate age- and sex-adjusted rates per 1000 person-years, we first fit Poisson models[30] to the pooled data, then standardized the fitted rate in the euthyroidism group to the overall age and sex distribution of the pooled sample. Finally, to obtain rates in the TSH groups consistent with the meta-analytic results, we multiplied the standardized rates in the euthyroidism group by the summary meta-analytic HRs. We checked the proportional hazard assumption using graphical methods and Schoenfeld tests (all P>.05). We used the Egger test[31] and age- and sex-adjusted funnel plots to assess for publication bias.

RESULTS

Among 4440 reports identified, 12 prospective studies met eligibility criteria (eFigure at http://www.jama.com) and 11 prospective cohorts in the United States, Europe, Australia, Brazil, and Japan agreed to provide individual participant data (**TABLE 1**). The final sample included 55 287 adults comprising 3450 with subclinical hypothyroidism (6.2%) and 51 837 with euthyroidism. Zero to 8.3% of participants reported thyroid hormone use at baseline (all excluded in 5 studies) and 0% to 12.6% reported thyroid hormone use during follow-up. The median follow-up ranged from 2.5 to 20 years, with total follow-up of 542 494 person-years.

All 11 cohort studies reported total and CHD deaths, and 7 studies also reported CHD events among 25 977 participants. For the quality of individual studies, all studies reported outcome adjudication without knowledge of thyroid status; 4 of 7 studies reporting CHD events used formal adjudication procedures[6-8,27]; and 4 of 11 studies reporting CHD deaths mainly used death certificates.[26,33-35] All studies had 5% or less loss to follow-up.

During follow-up, 9664 participants died (2168 of CHD) and 4470 participants had CHD events (among 7 studies). In age- and sex-adjusted analyses, the overall HR for participants with subclinical hypothyroidism compared with euthyroidism was 1.18 (95% CI, 0.99-1.42) for CHD events (24.0 vs 20.3/1000 person-years for participants with euthyroidism), 1.14 (95% CI, 0.99-1.32) for CHD mortality (5.5 vs 4.9/1000 person-years), and 1.09 (95% CI, 0.96-1.24) for total mortality (23.1 vs 21.1/1000 person-years; **FIGURE 1**). We found heterogeneity across studies for CHD events (I^2=59%) and total mortality (I^2=66%), but not for CHD mortality (I^2=0%). We subsequently examined whether heterogeneity was related to differences in risks by degree of subclinical hypothyroidism and age. The risk of CHD events (P<.001 for trend) and CHD death (P=.005 for trend) increased with higher TSH level, but not for total mortality (**FIGURE 2**). In stratified analyses, participants with TSH levels of 10 mIU/L or greater had significantly increased risk of CHD events (HR, 1.89 [95% CI, 1.28-2.80]; n=70 events/235; 38.4 vs 20.3/1000 person-years for participants with euthyroidism) and CHD mortality (HR, 1.58 [95% CI, 1.10-2.27]; n=28 deaths/333; 7.7 vs 4.9/1000 person-years) compared with participants with euthyroidism. The risk for CHD associated with subclinical hypothyroidism appeared to be somewhat higher in younger participants, but the number of outcomes in the younger age group was small, and there was no significant trend in CHD risk across age groups. Otherwise, the risk estimates for CHD events, CHD mortality, and total mortality did not differ significantly according to age, sex, race, or preexisting cardiovascular disease, except an increase in CHD events and CHD mortality among white but not among nonwhite participants with subclinical hypothyroidism (**TABLE 2**). All results were similar after further adjustment for traditional cardiovascular risk factors.

Sensitivity analyses yielded similar results, with increased risks of CHD events and mortality in those with TSH levels of 10 mIU/L or greater (**TABLE 3**). Risk estimates were slightly higher for those with TSH levels of 10 mIU/L or greater after excluding those who took thyroid medication during follow-up.

Estimates were lower for subclinical hypothyroidism overall after limiting the analyses to 4 studies with formal adjudication procedures, but slightly higher for those with TSH levels of 10 mIU/L or greater. The effect of increasing TSH level on CHD events did not significantly differ according to age ($P=.87$ for interaction). We found no evidence of publication bias, either with visual assessment of age- and sex-adjusted funnel plots or with the Egger test for mortality data ($P=.39$ for CHD mortality and $P=.97$ for total mortality) and little evidence of publication bias for CHD events ($P=.13$ for CHD events).

COMMENT

In this analysis of 55 287 individual participants from 11 prospective cohort studies, subclinical hypothyroidism was associated with an increased risk of CHD events and CHD mortality in those with higher TSH levels. There was a significant trend of increased risk at higher serum TSH concentrations, and the risk of both CHD mortality and CHD events was significantly increased in participants with TSH levels of 10 mIU/L or greater. These associations persisted after adjustment for traditional cardiovascular risk factors, and did not significantly differ by age, sex, race, or preexisting cardiovascular disease. Compared with participants with euthyroidism, the overall HR for CHD events with subclinical hypothyroidism was 1.18 (95% CI, 0.99-1.42) and the overall HR for CHD mortality was 1.14 (95% CI, 0.99-1.32). Minimal TSH elevations were not associated with an increased risk of CHD events and CHD mortality. Our results clarify the CHD risk of subgroups of adults with subclinical hypothyroidism, which could not be adequately addressed in previous study-level meta-analyses[10-12] or in single cohort studies performed in more lim-

Table 1. Baseline Characteristics of Individuals in Included Studies (N=55 287)

Study	Description of Study Sample	No.	Age, Median (Range), y[a]	No. (%)		Thyroid Medication Use, No. (%)		Follow-up[b]		
				Women	Subclinical Hypothyroidism	At Baseline[c]	During Follow-up	Start, y	Duration, Median (IQR), y	Person-Years
United States										
Cardiovascular Health Study,[6] 2006	CDAs with Medicare eligibility in 4 US communities	3003	71 (64-100)	1803 (60.0)	492 (16.4)	0	153 (5.1)	1989-1990	13.9 (8.7-16.4)	36 865
Health, Aging, and Body Composition Study,[7] 2005	CDAs aged 70-79 y with Medicare eligibility in 2 US communities	2660	74 (69-81)	1338 (50.3)	335 (12.6)	222 (8.3)	334 (12.6)	1997	8.3 (7.3-8.4)	19 410
Europe										
Birmingham Study,[26] 2001	CDAs aged ≥60 y from primary care practice in Birmingham, England	1098	68 (60-94)	622 (56.6)	92 (8.4)	0	28 (2.6)	1988	10.2 (5.9-10.6)	9030
EPIC-Norfolk Study,[32] 2010	Adults aged 45-79 y living in Norfolk, England	12 617	58 (39-78)	6828 (54.1)	720 (5.7)	0	NA	1995-1998	12.7 (12.0-13.6)	153 845
HUNT Study,[33] 2008	Adults aged >40 y living in Nord-Trøndelag County, Norway	24 590	55 (41-98)	16 744 (68.1)	814 (3.3)	0	NA	1995-1997	8.3 (7.9-8.9)	200 334
Leiden 85-plus Study,[27] 2004	All adults aged 85 y living in Leiden, the Netherlands	486	85 (NA)	318 (65.4)	35 (7.2)	14 (2.9)	16 (3.3)	1997-1999	5.2 (2.5-8.5)	2624
Pisa cohort,[8] 2007	Patients admitted to cardiology department in Pisa, Italy[d]	2875	63 (19-92)	921 (32.0)	228 (7.9)	12 (0.4)	0	2000-2006	2.5 (1.6-3.7)	7710
Whickham Survey,[17,18] 1996, 2010	Adults living in and near Newcastle upon Tyne, England	2406	46 (18-92)	1284 (53.4)	124 (5.2)	99 (4.1)	73 (3.0)	1972-1974	19 (15-20)	39 084
Australia										
Busselton Health Study,[9] 2005	Adults living in Busselton, Western Australia	1984	51 (18-90)	973 (49.0)	89 (4.5)	15 (0.8)	33 (1.7)	1981	20.0 (19.4-20.0)	35 158
Asia										
Nagasaki Adult Health Study,[34] 2004	Atomic bomb survivors in Nagasaki, Japan	2591	57 (38-92)	1586 (61.2)	420 (16.2)	33 (1.3)	6 (0.2)	1984-1987	13.1 (12.3-13.7)	31 559
South America										
Brazilian Thyroid Study,[35] 2010	Adults of Japanese descent living in São Paulo, Brazil	977	56 (30-92)	518 (53.0)	101 (10.3)	0	NA	1999-2000	7.3 (7.0-7.5)	6875

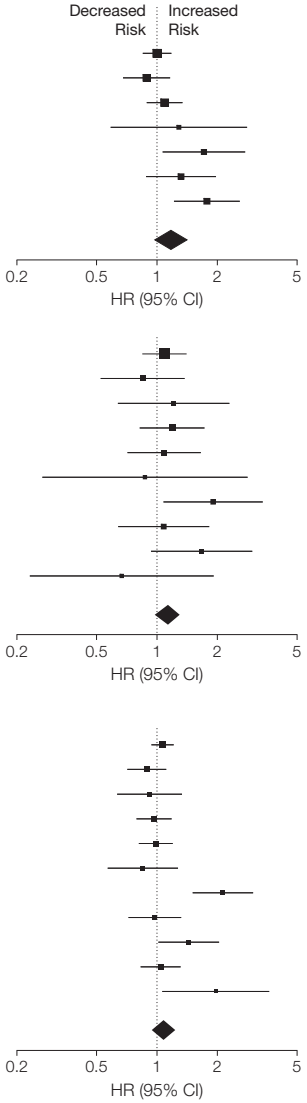
Abbreviations: CDA, community-dwelling adult; IQR, interquartile range (25th-75th percentiles); NA, data not available.
[a] Participants younger than 18 years were not included.
[b] For all cohorts, the maximal follow-up data that were available were used, which might differ from previous reports for some cohorts.
[c] The numbers of participants with thyroid medication use and thyroid-stimulating hormone levels of 10 mIU/L or greater were 12 of 222 in the Health, Aging, and Body Composition Study; 3 of 14 in the Leiden 85-plus Study; 12 of 12 in the Pisa cohort; 2 of 99 in the Whickham Survey; 2 of 15 in the Busselton Health Study; and 2 of 33 in the Nagasaki Adult Health Study.
[d] Excluded patients with acute coronary syndrome or severe illness.

ited age groups or without TSH stratification.[6,7,26,27]

These results are generally consistent with previous study-level meta-analyses showing modest increased risks of CHD events and cardiovascular mortality associated with subclinical hypothyroidism.[10,11] However, these meta-analyses could not accurately explore potential differences related to participant characteristics (eg, age, TSH concentrations) because of potential bias without individual participant data analysis (ecological fallacy),[13] and they also were limited by clinical heterogeneity,[10,36] with individual studies using varying TSH cutoffs, confounding factors for adjustment, and CHD definitions. Among 11 cohorts, only 2 studies previously reported results stratified by TSH level. One study[9] reported an increased risk of CHD events in participants with a TSH level of 10.0 mIU/L or greater (HR, 2.2; 95% CI, 1.2-4.2) and the other study[7] reported an increased risk of cardiovascular mortality (HR, 2.26; 95% CI, 0.54-9.45) but not CHD events (HR, 0.96; 95% CI, 0.35-2.61) over 4 years among adults aged 70 to 79 years with TSH levels of

Figure 1. Subclinical Hypothyroidism vs Euthyroidism for Coronary Heart Disease (CHD) Events, CHD Mortality, and Total Mortality[a]

	Subclinical Hypothyroidism		Euthyroidism			
CHD Events[b]	No. of Events	No. of Participants	No. of Events	No. of Participants	HR (95% CI)	Weight, %
Cardiovascular Health Study,[6] 2006	180	492	955	2511	1.00 (0.85-1.17)	22.9
Health, Aging, and Body Composition Study,[7] 2005	62	335	493	2325	0.89 (0.68-1.16)	17.4
EPIC-Norfolk Study,[32] 2010	103	720	1575	11897	1.09 (0.89-1.33)	20.8
Leiden 85-plus Study,[27] 2004	7	35	76	449	1.29 (0.59-2.80)	4.5
Pisa cohort,[8] 2007	20	228	148	2647	1.72 (1.07-2.74)	9.7
Whickham Survey,[17,18] 1996, 2010	27	121	438	2239	1.32 (0.89-1.96)	11.9
Busselton Health Study,[9] 2005	31	89	355	1889	1.78 (1.22-2.58)	12.8
Total (I^2 = 59%)	430	2020	4040	23957	1.18 (0.99-1.42)	100.0
CHD Mortality[c]						
Cardiovascular Health Study,[6] 2006	75	491	365	2511	1.09 (0.85-1.40)	33.8
Health, Aging, and Body Composition Study,[7] 2005	19	335	156	2325	0.85 (0.53-1.37)	9.2
Birmingham Study,[26] 2001	11	92	113	1006	1.21 (0.64-2.29)	5.2
EPIC-Norfolk Study,[32] 2010	31	720	422	11897	1.19 (0.83-1.72)	15.6
HUNT Study,[33] 2008	24	814	375	23776	1.09 (0.72-1.65)	12.1
Leiden 85-plus Study,[27] 2004	3	35	41	446	0.87 (0.27-2.82)	1.5
Pisa cohort,[8] 2007	14	228	92	2647	1.91 (1.08-3.36)	6.6
Whickham Survey,[17,18] 1996, 2010	16	124	223	2282	1.08 (0.64-1.81)	7.8
Busselton Health Study,[9] 2005	13	89	144	1892	1.67 (0.94-2.97)	6.3
Nagasaki Adult Health Study,[34] 2004	4	420	27	2171	0.67 (0.23-1.91)	1.9
Total (I^2 = 0%)	210	3348	1958	50953	1.14 (0.99-1.32)	100.0
Total Mortality						
Cardiovascular Health Study,[6] 2006	310	492	1514	2511	1.07 (0.95-1.21)	13.8
Health, Aging, and Body Composition Study,[7] 2005	92	335	699	2325	0.89 (0.72-1.11)	11.0
Birmingham Study,[26] 2001	32	92	435	1006	0.92 (0.64-1.33)	7.1
EPIC-Norfolk Study,[32] 2010	108	720	1716	11897	0.97 (0.80-1.18)	11.6
HUNT Study,[33] 2008	116	814	2159	23776	0.99 (0.82-1.19)	11.9
Leiden 85-plus Study,[27] 2004	26	35	364	451	0.85 (0.57-1.27)	6.4
Pisa cohort,[8] 2007	39	228	238	2647	2.13 (1.52-3.00)	7.6
Whickham Survey,[17,18] 1996, 2010	49	124	681	2282	0.98 (0.73-1.31)	8.7
Busselton Health Study,[9] 2005	36	89	479	1895	1.44 (1.02-2.03)	7.6
Nagasaki Adult Health Study,[34] 2004	94	420	409	2171	1.04 (0.83-1.31)	10.8
Brazilian Thyroid Study,[35] 2010	13	101	55	876	1.96 (1.07-3.61)	3.6
Total (I^2 = 66%)	915	3450	8749	51837	1.09 (0.96-1.24)	100.0



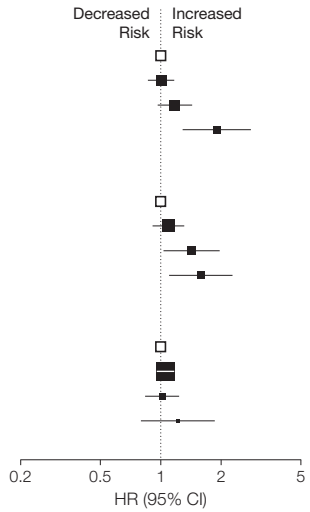
[a] The sizes of the data markers are proportional to the inverse variance of the hazard ratios (HRs). CI indicates confidence interval; HUNT, Nord-Trøndelag Health Study; HR, hazard ratio.
[b] Forty-six participants from the Whickham survey and 3 participants from the Busselton Health Study were not included because follow-up data were only available for death.
[c] Nine participants were excluded from the analysis because of missing cause of death. The Brazilian Thyroid Study was not included in this analysis because of unreliable estimates based on the small number of CHD deaths (n = 10).

10 mIU/L or greater. However, the HR for CHD events increased to 1.28 (95% CI, 0.68-2.39) with extended follow-up to 8 years in the present data. In overall pooled data, we found statistical heterogeneity among individual study findings for CHD events (I^2=59%), but not for CHD death. Part of the heterogeneity might be related to different CHD risks across age, race, and TSH subgroups.

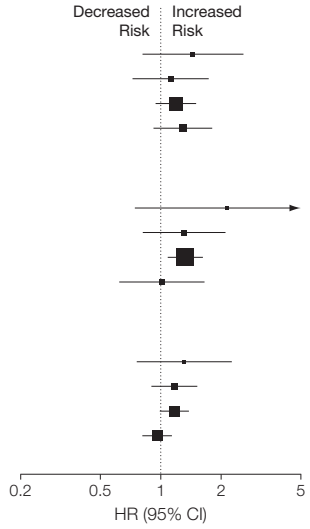
Our individual participant data analysis found that the CHD outcomes in adults with subclinical hypothyroidism did not differ significantly across age groups. For the specific age group of 80 years or older, there was no significant increased risk of total mortality, CHD mortality, or CHD events in contrast to a single previous study that found reduced mortality associated with increasing TSH concentrations.[27,37] Previous study-level meta-analyses have found increased risks of CHD events and cardiovascular mortality associated with subclinical hypothyroidism, particularly in studies with a mean age of younger than 65 years,[10,11] but this was not confirmed by our individual participant data analysis. We found some evidence for increased risks of CHD events and mor-

Figure 2. Hazard Ratios (HRs) for Coronary Heart Disease (CHD) Events, CHD Mortality, and Total Mortality According to Elevated Thyroid-Stimulating Hormone (TSH) Categories and Subclinical Hypothyroidism Stratified by Age vs Euthyroidism[a]

CHD Events by TSH Level, mIU/L[b]	No. of Events	No. of Participants	HR Ratio (95% CI)
0.5-4.49	4040	23957	1 [Reference]
4.5-6.9	264	1344	1.00 (0.86-1.18)
7.0-9.9	96	441	1.17 (0.96-1.43)
10-19.9	70	235	1.89 (1.28-2.80)
			P<.001 for trend
CHD Mortality by TSH Level, mIU/L[c]			
0.5-4.49	1958	50953	1 [Reference]
4.5-6.9	132	2363	1.09 (0.91-1.30)
7.0-9.9	50	652	1.42 (1.03-1.95)
10-19.9	28	333	1.58 (1.10-2.27)
			P = .005 for trend
Total Mortality by TSH Level, mIU/L[d]			
0.5-4.49	8749	51837	1 [Reference]
4.5-6.9	640	2431	1.06 (0.96-1.17)
7.0-9.9	170	672	1.02 (0.84-1.24)
10-19.9	105	347	1.22 (0.80-1.87)
			P = .39 for trend



	Subclinical Hypothyroidism		Euthyroidism		
CHD Events, by Age, y[b]	No. of Events	No. of Participants	No. of Events	No. of Participants	HR Ratio (95% CI)
18-49	12	221	272	5405	1.46 (0.82-2.62)
50-64	54	517	997	7876	1.13 (0.73-1.77)
65-79	322	1158	2511	9668	1.20 (0.95-1.51)
≥80	42	124	260	1008	1.30 (0.93-1.82)
					P = .78 for trend
CHD Mortality, by Age, y[c]					
18-49	2	444	54	13560	2.13 (0.74-6.14)
50-64	16	1072	316	18513	1.30 (0.81-2.08)
65-79	163	1608	1288	16567	1.32 (1.08-1.62)
≥80	29	224	300	2313	1.01 (0.62-1.63)
					P = .22 for trend
Total Mortality, by Age, y[d]					
18-49	14	465	340	13832	1.31 (0.76-2.26)
50-64	108	1121	1492	18875	1.17 (0.90-1.51)
65-79	623	1636	5316	16785	1.17 (0.99-1.39)
≥80	170	228	1601	2345	0.96 (0.81-1.12)
					P = .29 for trend



[a] The sizes of the filled square data markers are proportional to the inverse variance of the HRs. The unfilled squares indicate the reference categories. For the analyses stratified by age, the HRs for CHD events, CHD mortality, and total mortality were adjusted for sex and age as a continuous variable to avoid residual confounding within age strata. CI indicates confidence interval.
[b] Data were available from 7 studies.
[c] Data were available from 10 studies. The Brazilian Thyroid Study was not included because of unreliable estimates based on the small number of CHD deaths (n=10). Nine participants were excluded from the analysis because of missing cause of death.
[d] Data were available from 11 studies.

tality in younger adults with subclinical hypothyroidism, but there also were large 95% CIs without significant trend across age groups (Figure 2). Moreover, the effect of increasing TSH level on CHD events did not significantly differ according to age. In contrast to a previous study suggesting that adults with subclinical hypothyroidism and preexisting cardiovascular disease might be at particularly high cardiovascular risk,[8] we found no significant effect of baseline preexisting cardiovascular disease on outcomes.

The increased risk of CHD events associated with higher TSH levels in our study might be related to the known effects of thyroid hormone on the heart and metabolism, consistent with the concept that subclinical hypothyroidism is a milder form of overt hypothyroid-

Table 2. Stratified Analyses for the Associations Between Subclinical Hypothyroidism and Risk of Coronary Heart Disease (CHD) Events, CHD Mortality, and Total Mortality

	CHD Events[a]			CHD Mortality[b]			Total Mortality		
		HR (95% CI)			HR (95% CI)			HR (95% CI)	
	No. of Events/ Total Participants	Adjusted for Age and Sex	Multivariate Model[c]	No. of Events/ Total Participants	Adjusted for Age and Sex	Multivariate Model[c]	No. of Events/ Total Participants	Adjusted for Age and Sex	Multivariate Model[c]
Total population	4470/25 977	1.18 (0.99-1.42)	1.18 (0.99-1.40)	2168/54 301	1.14 (0.99-1.32)	1.15 (0.99-1.34)	9664/55 287	1.09 (0.96-1.24)	1.13 (0.98-1.29)
Men[d]	2642/12 531	1.06 (0.90-1.25)	1.06 (0.91-1.25)	1246/21 889	1.14 (0.90-1.43)	1.12 (0.90-1.39)	4851/22 352	1.13 (0.93-1.36)	1.14 (0.93-1.39)
Women[d]	1828/13 446	1.21 (0.99-1.48)	1.23 (0.99-1.52)	922/32 412	1.21 (0.99-1.47)	1.24 (1.01-1.53)	4813/32 935	1.06 (0.95-1.19)	1.09 (0.98-1.21)
P for interaction		.32	.27		.71	.51		.58	.70
Age, y[e]									
18-49	284/5626	1.46 (0.82-2.62)	1.55 (0.87-2.78)	56/14 004	2.13 (0.74-6.14)	2.49 (0.87-7.19)	354/14 297	1.31 (0.76-2.26)	1.44 (0.84-2.48)
50-64	1051/8393	1.13 (0.73-1.77)	1.11 (0.75-1.66)	332/19 585	1.30 (0.81-2.08)	1.32 (0.79-2.18)	1600/19 996	1.17 (0.90-1.51)	1.22 (0.91-1.65)
65-79	2833/10 826	1.20 (0.95-1.51)	1.21 (0.96-1.52)	1451/18 175	1.32 (1.08-1.62)	1.33 (1.07-1.65)	5939/18 421	1.17 (0.99-1.39)	1.22 (1.03-1.45)
≥80	302/1132	1.30 (0.93-1.82)	1.24 (0.89-1.73)	329/2537	1.01 (0.62-1.63)	0.98 (0.60-1.60)	1771/2573	0.96 (0.81-1.12)	0.94 (0.80-1.11)
P for trend		.78	.58		.22	.12		.29	.15
Race[f]									
White	4193/24 746	1.20 (1.02-1.42)	1.20 (1.02-1.40)	1905/49 381	1.18 (1.01-1.38)	1.19 (1.02-1.39)	8142/49 390	1.10 (0.94-1.28)	1.11 (0.95-1.29)
Black	277/1231	0.75 (0.48-1.19)	0.73 (0.46-1.17)	108/1231	0.67 (0.31-1.44)	0.59 (0.25-1.37)	484/1231	0.94 (0.69-1.29)	0.96 (0.70-1.32)
Asian	NA	NA	NA	31/2591	0.67 (0.23-1.91)	0.67 (0.23-1.95)	571/3568	1.34 (0.73-2.46)	1.39 (0.78-2.46)
P for interaction		.05	.05		.23	.18		.52	.51
TSH, mIU/L									
0.5-4.49	4040/23 957	1 [Reference]	1 [Reference]	1958/50 953	1 [Reference]	1 [Reference]	8749/51 837	1 [Reference]	1 [Reference]
4.5-6.9	264/1344	1.00 (0.86-1.18)	1.01 (0.86-1.18)	132/2363	1.09 (0.91-1.30)	1.06 (0.88-1.28)	640/2431	1.06 (0.96-1.17)	1.07 (0.96-1.20)
7.0-9.9	96/441	1.17 (0.96-1.43)	1.22 (0.99-1.49)	50/652	1.42 (1.03-1.95)	1.53 (1.13-2.07)	170/672	1.02 (0.84-1.24)	1.11 (0.92-1.33)
10.0-19.9	70/235	1.89 (1.28-2.80)	1.86 (1.22-2.82)	28/333	1.58 (1.10-2.27)	1.54 (1.07-2.23)	105/347	1.22 (0.80-1.87)	1.24 (0.82-1.87)
P for trend		<.001	.002		.005	.005		.39	.29
Cardiovascular disease[g]									
Yes	1282/4263	1.17 (0.94-1.47)	1.09 (0.90-1.31)	590/4390	1.30 (0.98-1.72)	1.28 (0.99-1.66)	1649/4523	1.08 (0.87-1.34)	1.05 (0.86-1.29)
No	3142/21 391	1.16 (0.95-1.40)	1.18 (0.97-1.43)	1450/48 776	1.08 (0.89-1.30)	1.10 (0.91-1.33)	7532/49 629	1.10 (0.95-1.28)	1.13 (0.97-1.31)
P for interaction		.96	.57		.29	.35		.89	.57

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, data not applicable; TSH, thyroid-stimulating hormone.
[a] Data were available from 7 studies. Forty-six participants from the Whickham survey and 3 participants from the Busselton Health Study were not included in the analysis of CHD events because follow-up data were only available for death.
[b] Nine participants were excluded from this analysis because of missing cause of death. The Brazilian Thyroid Study was not included in this analysis because of unreliable estimates due to the low number of CHD deaths (n=10).
[c] Adjusted for sex, age, systolic blood pressure, current and former smoking, total cholesterol, and prevalent diabetes at baseline. The Birmingham Study was not included in this analysis because of lack of data on cardiovascular risk factors.
[d] These HRs were not adjusted for sex.
[e] These HRs were adjusted for sex and age as a continuous variable to avoid residual confounding within age strata.
[f] Data were not available for the Birmingham study (n=1098).
[g] Data were not available for the Birmingham study (n=1098). Thirty-seven participants with missing information on baseline cardiovascular disease from other studies were excluded from this analysis. For analysis of CHD events, 286 participants without preexisting cardiovascular disease from the Leiden 85-plus Study were further excluded because of no CHD event.

ism.[38,39] Increased systemic vascular resistance, arterial stiffness, altered endothelial function, increased atherosclerosis, and altered coagulability have been reported to be associated with subclinical hypothyroidism and may accelerate development of CHD.[4,39,40] The fact that adjustment for traditional cardiovascular risk factors did not alter risks could favor this hypothesis. Other potential mechanisms include elevated cholesterol level,[4,39] although adjustment for

Table 3. Sensitivity Analysis of the Effect of Subclinical Hypothyroidism on the Risk of Coronary Heart Disease (CHD) Events and CHD Mortality[a]

	CHD Events by Thyroid-Stimulating Hormone Level, mIU/L[b]					CHD Mortality by Thyroid-Stimulating Hormone Level, mIU/L				
		Subclinical Hypothyroidism					Subclinical Hypothyroidism			
		4.5-19.9		10-19.9			4.5-19.9		10-19.9	
	No. of Events/ Participants With Euthyroidism, 0.5-4.49	No. of Events/ Participants	HR (95% CI)	No. of Events/ Participants	HR (95% CI)	No. of Events/ Participants With Euthyroidism, 0.5-4.49	No. of Events/ Participants	HR (95% CI)	No. of Events/ Participants	HR (95% CI)
Random-effects model	4040/23 957	430/2020	1.18 (0.99-1.42)	70/235	1.89 (1.28-2.80)	1958/50 953	210/3348	1.14 (0.99-1.32)	28/333	1.58 (1.10-2.27)
Fixed-effects model	4040/23 957	430/2020	1.10 (0.99-1.22)	70/235	1.81 (1.43-2.30)	1958/50 953	210/3348	1.14 (0.99-1.32)	28/333	1.58 (1.10-2.27)
Excluding those with subclinical hypothyroidism										
With thyroid medication use[c]										
At baseline	3972/23 682	412/1937	1.16 (0.97-1.38)	60/204	1.77 (1.13-2.76)	1924/50 653	204/3253	1.14 (0.99-1.32)	24/300	1.46 (0.99-2.17)
At baseline and during follow-up	2354/11 635	246/998	1.17 (0.91-1.50)	29/73	2.17 (1.19-3.93)	1114/14 829	130/1466	1.25 (1.04-1.51)	15/90	1.85 (1.13-3.05)
With missing free thyroxine (T_4)[d]	4040/23 957	423/1995	1.19 (0.99-1.42)	70/232	1.85 (1.22-2.80)	1958/50 953	204/3303	1.15 (0.99-1.33)	28/330	1.55 (1.07-2.25)
Outcomes										
Excluding soft CHD outcomes[e]	3393/23 957	334/2020	1.23 (1.04-1.46)	53/235	1.81 (1.10-2.98)			NA		NA
Studies with formal adjudication procedures[6-8,27,f]	1672/7932	269/1090	1.08 (0.85-1.37)	41/113	2.05 (1.14-3.68)	654/7929	111/1089	1.13 (0.83-1.55)	16/112	1.77 (1.08-2.89)
Adjustments[g]										
Cardiovascular risk factors										
Plus lipid-lowering and antihypertensive medications	2465/12 060	327/1300	1.23 (0.97-1.57)	55/155	1.90 (1.09-3.34)	1396/35 879	164/2116	1.14 (0.96-1.35)	24/236	1.57 (1.04-2.37)
Plus BMI	4040/23 957	430/2020	1.16 (0.98-1.37)	70/235	1.86 (1.22-2.85)	1845/49 947	199/3256	1.13 (0.97-1.32)	28/316	1.45 (0.99-2.13)
Studies Excluded										
Study of cardiac patients[8]	3892/21 310	410/1792	1.13 (0.95-1.34)	64/212	1.66 (1.19-2.31)[h]	1866/48 306	196/3120	1.10 (0.95-1.28)	26/310	1.53 (1.05-2.23)[h]
Atomic bomb survivors in Nagasaki, Japan[34]			NA[i]		NA[i]	1931/48 782	206/2928	1.15 (1.00-1.34)	28/318	1.57 (1.09-2.26)
HUNT Study[33,j]			NA[i]		NA[i]	1583/27 177	186/2534	1.15 (0.99-1.34)	28/268	1.61 (1.12-2.33)
Additional Study Considered										
Rotterdam Study,[5,k]	4050/24 807	434/2127	1.20 (1.00-1.44)		NA[l]			NA[l]		NA[l]

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; HR, hazard ratio; NA, data not applicable.
[a] The HRs were adjusted for age and sex using a random-effects model.
[b] Data were available from 7 studies.
[c] The numbers of participants with thyroid medication use appear in columns 7 and 8 of Table 1. The HUNT Study and the EPIC-Norfolk Study were not included in this analysis because of lack of this information during follow-up.
[d] The numbers of participants appear in the eTable at http://www.jama.com.
[e] Defined as hospitalization for angina or revascularization (coronary angioplasty or surgery) and participants with these outcomes were excluded from this analysis, which was possible for participants from 4 studies (eTable). In contrast, hard events were defined as nonfatal myocardial infarction or CHD death, as defined in the current Framingham risk score.[20]
[f] Defined as having clear criteria for the outcomes that were reviewed by experts for each potential case (eg, specific electrocardiogram or cardiac enzymes modifications for CHD). For this analysis, CHD adjudication based only on death certificates was not considered as a formal adjudication procedure.
[g] The Birmingham Study was excluded from these analyses because of lack of data on cardiovascular risk factors. Data on lipid-lowering and antihypertensive medications were not available for the EPIC-Norfolk and Nagasaki Adult Health studies.
[h] With further adjustment for cardiovascular risk factors after excluding the Pisa cohort, the HRs for TSH level of 10-19.9 mIU/L were 1.63 (95% CI, 1.13-2.34) for CHD events, 1.52 (95% CI, 1.04-2.23) for CHD mortality, and 1.05 (95% CI, 0.79-1.40) for total mortality (vs an HR of 1.06 [95% CI, 0.83-1.35] in age- and sex-adjusted analyses excluding the Pisa cohort).
[i] No data on CHD events were available.
[j] Had the lowest rate of subclinical hypothyroidism (3.3%, Table 1).
[k] This study had 14 CHD events[5,10] but did not accept invitation to share individual participant data. Summary estimates of this study, adjusted for age, BMI, total cholesterol, high-density lipoprotein cholesterol, blood pressure, and smoking were used in the random-effect models as a sensitivity analysis.[24]
[l] The TSH subgroups were not reported in the study.

cholesterol level did not remove the associations in our data. Adults with higher TSH concentrations also are more likely to develop overt hypothyroidism,[41] and it is possible that this progression explains the association with subclinical hypothyroidism. Alternative explanations for the observed results are bias in the selection of included studies, bias and quality problems in the original studies, publication bias, and unmeasured confounders.[42] Sensitivity analyses pooling higher-quality studies yielded similar results. Whereas one randomized controlled trial has shown benefits with thyroxine treatment of subclinical hypothyroidism on intima-media thickness[40] and another has shown benefits with thyroxine treatment of subclinical hypothyroidism on brachial artery endothelial function,[43] the potential causal relationship can only be proven by randomized controlled trials of thyroxine replacement and clinical outcomes.[36]

Among the strengths of our study, an individual participant data analysis is the preferred way to perform time-to-event analyses to avoid biases associated with the use of aggregate data in meta-regression for subgroup analysis and to allow standardization of definitions of predictors, outcomes, and adjustment for potential confounders.[14,22] We included all available international and published data on these associations. Among the limitations of our study, the individual participant data analysis included predominantly white populations, except for 2 studies conducted in Japan[34] and Brazil.[35] Results for subgroups at risk of CHD mortality generally had wider 95% CIs than those for CHD events, reflecting less statistical power. However, post hoc calculations showed 80% power to detect meaningful differences between overall subclinical hypothyroidism and euthyroidism groups for each outcome. Specifically, our study had adequate power to detect an HR of 1.18 or higher for CHD events, an HR of 1.30 or higher for CHD mortality, and an HR of 1.13 or higher for total mortality. Even with this very large amount of individual participant data, our power for subgroup analyses was limited among those with TSH levels of 10 mIU/L or greater or adults younger than 50 years because of the limited number of CHD events and deaths. Thyroid function testing was performed only at baseline, and we have no data on how many participants progressed from euthyroidism to subclinical hypothyroidism, from subclinical to overt hypothyroidism, or who normalized their TSH level over time, which is a limitation of all published large cohorts.[6,7,33] In addition, free triiodothyronine (T_3) was not available in most cohorts, and thus could not be included in thyroid status classification. Commencement of thyroid medication during follow-up by up to 12.6% of participants might have attenuated any true effects of subclinical hypothyroidism, as illustrated by the sensitivity analysis excluding such participants.

In summary, combining all available data from large prospective cohorts among 55 287 individual participants suggests that subclinical hypothyroidism is associated with an increased risk of CHD in those with higher TSH levels. The risk of both CHD mortality and CHD events, but not of total mortality, increases with higher concentrations of TSH and is significantly elevated in adults with TSH levels of 10 mIU/L or greater. Conversely, minimal TSH elevations are not associated with an increased risk of CHD events and CHD mortality. Our finding of no increased risk of CHD among the high proportions of adults with minimal TSH elevations is also important because many patients with minimal TSH elevations are currently treated in clinical practice.[44] Our results might help refine a TSH threshold at which larger clinical benefits of thyroxine replacement would be expected.[4,45] Our study cannot address whether these risks are attenuated or abolished by thyroxine replacement. Given the high prevalence of subclinical hypothyroidism,[2,19] this question needs to be addressed in an appropriately powered randomized controlled trial.

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Author Contributions: Dr Rodondi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Rodondi, Bauer, Walsh, Åsvold, Iervasi, Imaizumi, Sgarbi, Khaw, Vanderpump, Newman, Franklyn, Westendorp, Gussekloo.

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