



Universiteit
Leiden
The Netherlands

Subclinical Hypothyroidism and the Risk of Coronary Heart Disease and Mortality

Rodondi, N.; Elzen, W.P.J. den; Bauer, D.C.; Cappola, A.R.; Razvi, S.; Walsh, J.P.; ... ; Thyroid Studies Collaboration

Citation

Rodondi, N., Elzen, W. P. J. den, Bauer, D. C., Cappola, A. R., Razvi, S., Walsh, J. P., ... Gussekloo, J. (2010). Subclinical Hypothyroidism and the Risk of Coronary Heart Disease and Mortality. *Journal Of The American Medical Association*, 304(12), 1365-1374.
doi:10.1001/jama.2010.1361

Version: Not Applicable (or Unknown)
License: [Leiden University Non-exclusive license](#)
Downloaded from: <https://hdl.handle.net/1887/117571>

Note: To cite this publication please use the final published version (if applicable).

Subclinical Hypothyroidism and the Risk of Coronary Heart Disease and Mortality

Nicolas Rodondi, MD, MAS
Wendy P. J. den Elzen, MSc
Douglas C. Bauer, MD
Anne R. Cappola, MD, ScM
Salman Razvi, MD, FRCP
John P. Walsh, MBBS, FRACP, PhD
Bjørn O. Åsvold, MD, PhD
Giorgio Iervasi, MD
Misa Imaizumi, MD, PhD
Tinh-Hai Collet, MD
Alexandra Bremner, PhD
Patrick Maisonneuve, Ing
José A. Sgarbi, MD
Kay-Tee Khaw, MD
Mark P. J. Vanderpump, MD, FRCP
Anne B. Newman, MD, MPH
Jacques Cornuz, MD, MPH
Jayne A. Franklyn, MD, PhD, FRCP
Rudi G. J. Westendorp, MD, PhD
Eric Vittinghoff, PhD
Jacobijn Gussekloo, MD, PhD
for the Thyroid Studies Collaboration

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 (T₄) concentrations. Because subclinical hypothyroidism has been associated with hypercholesterolemia⁴ and atherosclerosis,⁵

See also Patient Page.



CME available online at
www.jamaarchivescme.com
and questions on p 1392.

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.

JAMA. 2010;304(12):1365-1374

www.jama.com

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-analyses¹⁰⁻¹² found modestly increased

risks for CHD and mortality, but with heterogeneity among individual studies that used different TSH cutoffs, dif-

Author Affiliations are listed at the end of this article.
Corresponding Author: Nicolas Rodondi, MD, MAS, Department of Ambulatory Care and Community Medicine, University of Lausanne, Bugnon 44, 1011 Lausanne, Switzerland (Nicolas.Rodondi@hospvd.ch).

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 FT₄ 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 score²⁰) 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 criteria¹⁰ and new information from study authors, we systematically evaluated the following key indicators of study quality¹³: 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 study²⁷). For these study-specific analyses, we used penalized likelihood methods²⁸ 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 exclud-

ing 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 models³⁰ 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 test³¹ 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-analyses¹⁰⁻¹² 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.

^aParticipants younger than 18 years were not included.

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

^cThe 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.

^dExcluded patients with acute coronary syndrome or severe illness.

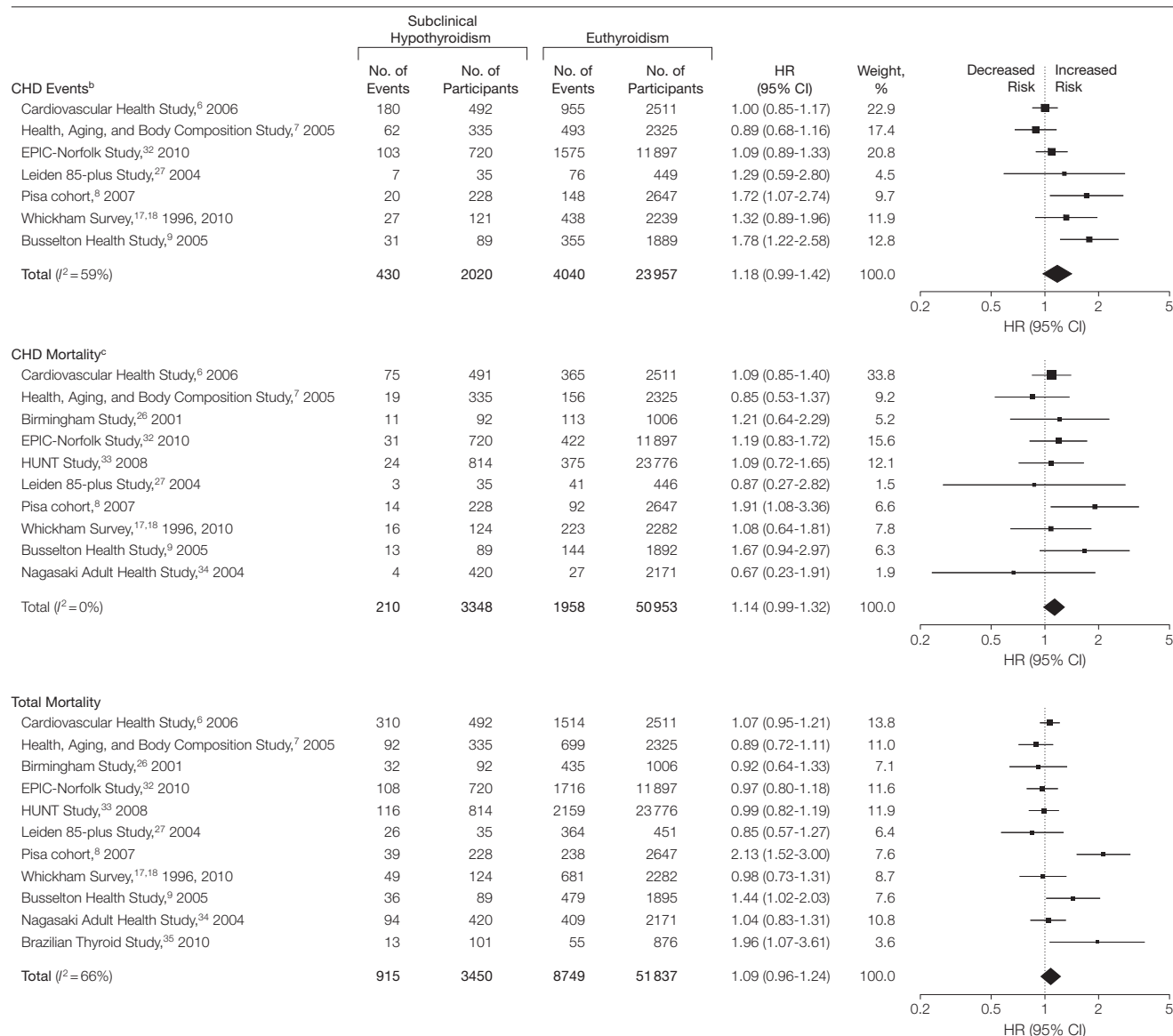
ited age groups or without TSH stratification.^{6,7,26,27}

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 study⁹ 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 study⁷ 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



^aThe 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.

^bForty-six participants from the Whickham survey and 3 participants from the Busseton Health Study were not included because follow-up data were only available for death.

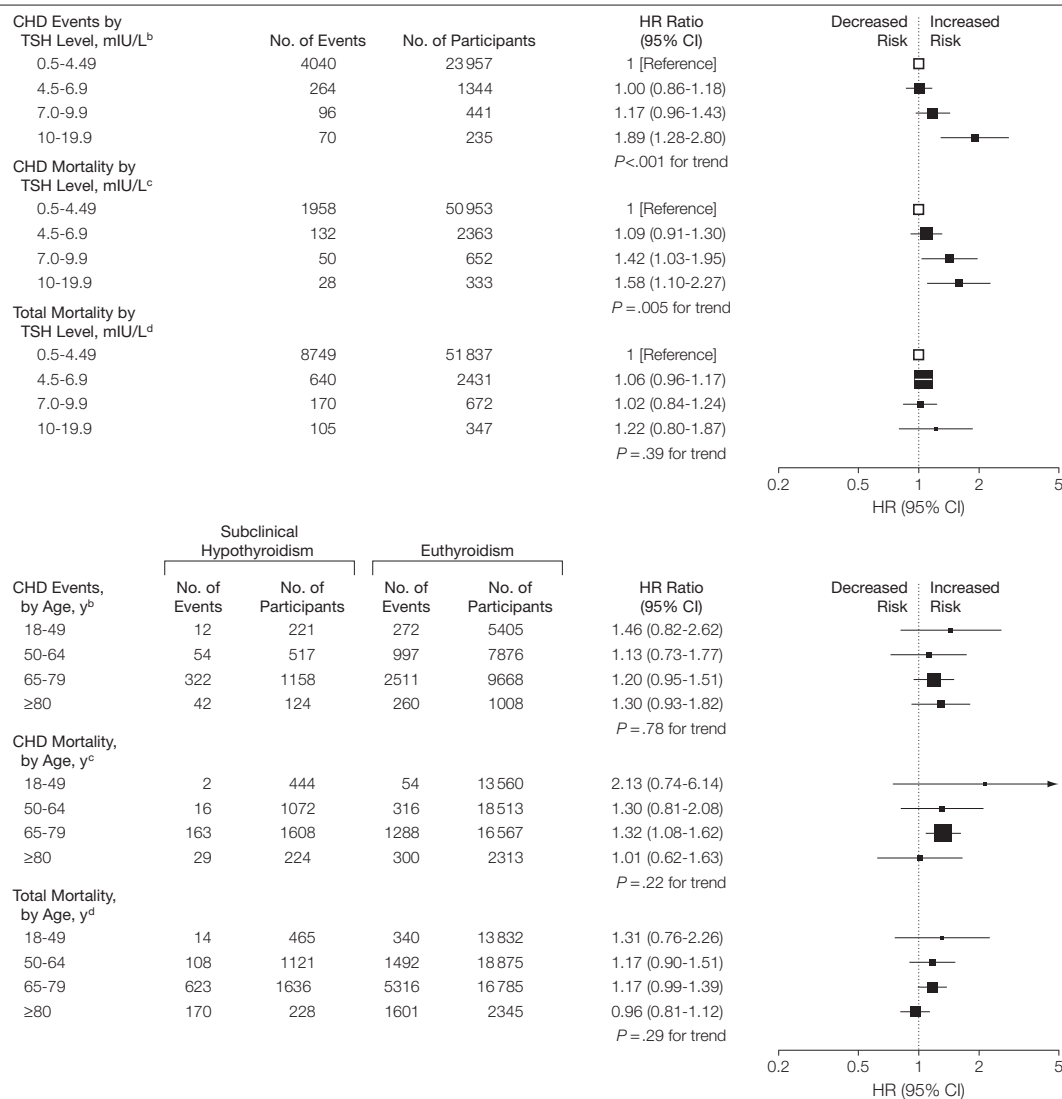
^cNine participants were excluded from the analysis because of missing cause of death. The Brazilian Thyroid Study was not included in this analysis because of unreliable estimates based on the small number of CHD deaths ($n = 10$).

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 increas-

ing 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



^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		
	No. of Events/ Total Participants	HR (95% CI)		No. of Events/ Total Participants	HR (95% CI)		No. of Events/ Total Participants	HR (95% CI)	
		Adjusted for Age and Sex	Multivariate Model ^c		Adjusted for Age and Sex	Multivariate Model ^c		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)
<i>P</i> 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)
<i>P</i> 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)
<i>P</i> 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)
<i>P</i> 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)
<i>P</i> for interaction		.96	.57		.29	.35		.89	.57

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, data not applicable; TSH, thyroid-stimulating hormone.

^aData 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.

^bNine 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).

^cAdjusted 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.

^dThese HRs were not adjusted for sex.

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

^fData were not available for the Birmingham study (*n* = 1098).

^gData 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 cardiovascu-

lar 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				
	No. of Events/ Participants With Euthyroidism, 0.5-4.49	Subclinical Hypothyroidism				No. of Events/ Participants With Euthyroidism, 0.5-4.49	Subclinical Hypothyroidism			
		4.5-19.9		10-19.9			4.5-19.9		10-19.9	
		No. of Events/ Participants	HR (95% CI)	No. of Events/ Participants	HR (95% CI)		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 ⁱ			NA ⁱ		NA ⁱ

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.

^aThe HRs were adjusted for age and sex using a random-effects model.

^bData were available from 7 studies.

^cThe 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.

^dThe numbers of participants appear in the eTable at <http://www.jama.com>.

^eDefined 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

^fDefined 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.

^gThe 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.

^hWith 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).

ⁱNo data on CHD events were available.

^jHad the lowest rate of subclinical hypothyroidism (3.3%, Table 1).

^kThis 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

^lThe 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 thickness⁴⁰ 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 Japan³⁴ 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 (T₃) 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.

Author Affiliations: Department of Ambulatory Care and Community Medicine, University of Lausanne, Lausanne, Switzerland (Drs Rodondi, Collet, and Cornuz); Departments of Public Health and Primary Care (Ms den Elzen and Dr Gussekloo) and Gerontology and Geri-

atrics (Dr Westendorp), Leiden University Medical Center, Leiden, the Netherlands; Departments of Medicine, Epidemiology, and Biostatistics (Drs Bauer and Vittinghoff) and Medicine (Dr Bauer), University of California, San Francisco; Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, School of Medicine, University of Pennsylvania, Philadelphia (Dr Cappola); Department of Endocrinology, Gateshead Health Foundation NHS Trust, Gateshead, England (Dr Razvi); Department of Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Nedlands, Western Australia (Dr Walsh); Schools of Medicine and Pharmacology (Dr Walsh) and Population Health (Dr Bremner), University of Western Australia, Crawley; Department of Public Health, Norwegian University of Science and Technology, Trondheim, Norway (Dr Åsvold); National Council Research Institute of Clinical Physiology, Pisa, Italy (Dr Iervasi); Department of Clinical Studies, Radiation Effects Research Foundation, Nagasaki, Japan (Dr Imaizumi); Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy (Mr Maisonneuve); Division of Endocrinology, Department of Medicine, Federal University of Sao Paulo, Brazil (Dr Sgarbi); Division of Endocrinology, Faculdade de Medicina de Marília, Marília, Brazil (Dr Sgarbi); Department of Public Health and Primary Care, University of Cambridge, Cambridge, England (Dr Khaw); Department of Endocrinology, Royal Free Hospital, London, England (Dr Vanderpump); Department of Epidemiology, University of Pittsburgh, Pittsburgh, Pennsylvania (Dr Newman); School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham, Birmingham, England (Dr Franklyn); and the Netherlands Consortium for Healthy Ageing, Leiden (Dr Westendorp).

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.

Study concept and design: Rodondi, Bauer, Cornuz, Westendorp, Gussekloo.

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

Analysis and interpretation of data: Rodondi, den Elzen, Bauer, Cappola, Razvi, Åsvold, Iervasi, Imaizumi, Collet, Bremner, Maisonneuve, Sgarbi, Cornuz, Franklyn, Westendorp, Vittinghoff, Gussekloo.

Drafting of the manuscript: Rodondi.

Critical revision of the manuscript for important intellectual content: den Elzen, Bauer, Cappola, Razvi, Walsh, Åsvold, Iervasi, Imaizumi, Collet, Bremner, Maisonneuve, Sgarbi, Khaw, Vanderpump, Newman, Cornuz, Franklyn, Westendorp, Vittinghoff, Gussekloo.

Statistical analysis: Rodondi, den Elzen, Bauer, Vittinghoff. **Obtained funding:** Walsh, Iervasi, Sgarbi, Khaw, Vanderpump, Newman, Franklyn, Westendorp, Gussekloo.

Administrative, technical, or material support: Rodondi, Collet, Khaw, Newman, Gussekloo.

Study supervision: Rodondi, Westendorp, Gussekloo.

Financial Disclosures: None reported.

Funding/Support: The Cardiovascular Health Study and the research reported in this article were supported by contract numbers N01-HC-80007, N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01-HC-15103, N01-HC-55222, N01-HC-75150, N01-HC-45133, grant number U01 HL080295 from the National Heart, Lung, and Blood Institute, with additional funding from the National Institute of Neurological Disorders and Stroke. Additional support was provided through grants R01 AG-15928, R01 AG-20098, AG-027058, and AG-032317 from the National Institute on Aging, grant R01 HL-075366 from the National Heart, Lung, and Blood Institute, and grant P30-AG-024827 from the University of Pittsburgh Claude D. Pepper Older Americans Independence Center. A full list of principal investigators and institutions of the Car-

diovascular Health Study can be found at <http://www.chs-nhlbi.org/pi.htm>. The thyroid measurements in the Cardiovascular Health Study were supported by an American Heart Association Grant-in-Aid (to Linda Fried). The Health, Aging, and Body Composition Study is supported by National Institute on Aging contract numbers N01-AG-6-2101, N01-AG-6-2103, and N01-AG-6-2106, and in part by the Intramural Research Program of the National Institutes of Health. The National Institute on Aging funded the Health Aging, and Body Composition study. The Leiden 85-plus Study was partly funded by the Dutch Ministry of Health, Welfare, and Sports. The Whickham Survey was supported by the UK Department of Health. The HUNT Study was a collaborative effort of the Faculty of Medicine, Norwegian University of Science and Technology, the Norwegian Institute of Public Health, and the Nord-Trøndelag County Council. The thyroid testing in the HUNT Study was financially supported by Wallac Oy (Turku, Finland). The Nagasaki Adult Health Study was supported by the Radiation Effects Research Foundation, Hiroshima and Nagasaki, Japan, a private, nonprofit foundation funded by the Japanese Ministry of Health, Labor and Welfare and the US Department of Energy, the latter in part through the National Academy of Sciences. This publication was supported by research protocol A-10-08 from the Radiation Effects Research Foundation. The EPIC-Norfolk study was supported by research grants from the UK Medical Research Council and the UK Cancer Research. The Brazilian Thyroid Study was supported by an unrestricted grant from the Sao Paulo State Research Foundation (Fundação de Amparo à Pesquisa do Estado de São Paulo grant 6/59737-9 to Rui Maciel). Dr Newman is supported by grant AG-023629 from the National Institute on Aging. Dr Westendorp is supported by grant NGI/NWO 911-03-016 from the Netherlands Organization for Scientific Research.

Role of the Sponsor: The majority of the sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript. The National Institute on Aging funded the Health, Aging, and Body Composition study and reviewed the manuscript and approved its publication. The Radiation Effects Research Foundation funded the Nagasaki Adult Health Study and reviewed the manuscript and approved its publication.

Statistical Evaluation: Dr Vittinghoff, professor of biostatistics, in the Department of Epidemiology and Biostatistics, University of California, San Francisco, reviewed the statistical analyses of the article.

Participating Studies of the Thyroid Studies Collaboration: *United States:* Cardiovascular Health Study; Health, Aging, and Body Composition Study. *The Netherlands:* the Leiden 85-plus Study. *Australia:* Busselton Health Study. *United Kingdom:* Whickham Survey; Birmingham Study; EPIC-Norfolk Study. *Italy:* Pisa Cohort. *Japan:* Nagasaki Adult Health Study. *Brazil:* Brazilian Thyroid Study. *Norway:* Nord-Trøndelag Health Study (HUNT Study).

Online-Only Material: eMethods, eTable, and eFigure are available at <http://www.jama.com>.

Additional Contributions: We thank Sabrina Molinaro (Clinical Physiology Institute, Pisa, Italy) for technical help about data from the Pisa Cohort and from Rui Maciel (Escola Paulista de Medicina, Federal University of São Paulo, Brazil) for technical help about data from the Brazilian Thyroid Study. The persons listed in this section did not receive financial compensation.

REFERENCES

1. Helfand M; US Preventive Services Task Force. Screening for subclinical thyroid dysfunction in non-pregnant adults. *Ann Intern Med.* 2004;140(2):128-141.

2. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease. *JAMA.* 2004;291(2):228-238.
3. Gharib H, Tuttle RM, Baskin HJ, et al. Subclinical thyroid dysfunction. *J Clin Endocrinol Metab.* 2005;90(1):581-585.
4. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. *Endocr Rev.* 2008;29(1):76-131.
5. Hak AE, Pols HA, Visser TJ, et al. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women. *Ann Intern Med.* 2000;132(4):270-278.
6. Cappola AR, Fried LP, Arnold AM, et al. Thyroid status, cardiovascular risk, and mortality in older adults. *JAMA.* 2006;295(9):1033-1041.
7. Rodondi N, Newman AB, Vittinghoff E, et al. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. *Arch Intern Med.* 2005;165(21):2460-2466.
8. Iervasi G, Molinaro S, Landi P, et al. Association between increased mortality and mild thyroid dysfunction in cardiac patients. *Arch Intern Med.* 2007;167(14):1526-1532.
9. Walsh JP, Bremner AP, Bulsara MK, et al. Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. *Arch Intern Med.* 2005;165(21):2467-2472.
10. Ochs N, Auer R, Bauer DC, et al. Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. *Ann Intern Med.* 2008;148(11):832-845.
11. Razvi S, Shakoor A, Vanderpump M, et al. The influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease. *J Clin Endocrinol Metab.* 2008;93(8):2998-3007.
12. Völzke H, Schwahn C, Wallaschofski H, Dörr M. Review: the association of thyroid dysfunction with all-cause and circulatory mortality. *J Clin Endocrinol Metab.* 2007;92(7):2421-2429.
13. Egger M, Davey Smith G, Schneider M, Minder C. *Systematic Reviews in Health Care: Meta-analysis in Context.* London, England: BMJ Publishing Group; 2001.
14. Simmonds MC, Higgins JP, Stewart LA, et al. Meta-analysis of individual patient data from randomized trials. *Clin Trials.* 2005;2(3):209-217.
15. Rodondi N, Bauer DC, Cappola AR, et al. Subclinical thyroid dysfunction, cardiac function, and the risk of heart failure. *J Am Coll Cardiol.* 2008;52(14):1152-1159.
16. Nicoloff JT, Spencer CA. Clinical review 12: the use and misuse of the sensitive thyrotropin assays. *J Clin Endocrinol Metab.* 1990;71(3):553-558.
17. Vanderpump MP, Tunbridge WM, French JM, et al. The development of ischemic heart disease in relation to autoimmune thyroid disease in a 20-year follow-up study of an English community. *Thyroid.* 1996;6(3):155-160.
18. Razvi S, Weaver JU, Vanderpump MP, Pearce SH. The incidence of ischemic heart disease and mortality in people with subclinical hypothyroidism: reanalysis of the Whickham Survey cohort. *J Clin Endocrinol Metab.* 2010;95(4):1734-1740.
19. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994). *J Clin Endocrinol Metab.* 2002;87(2):489-499.
20. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285(19):2486-2497.
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7(3):177-188.
22. Stewart LA, Clarke MJ; Cochrane Working Group. Practical methodology of meta-analyses (overviews) using updated individual patient data. *Stat Med.* 1995;14(19):2057-2079.
23. Fowkes FG, Murray GD, Butcher I, et al; Ankle

- Brachial Index Collaboration. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality. *JAMA.* 2008;300(2):197-208.
24. Riley RD, Simmonds MC, Look MP. Evidence synthesis combining individual patient data and aggregate data. *J Clin Epidemiol.* 2007;60(5):431-439.
25. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557-560.
26. Parle JV, Maisonneuve P, Sheppard MC, et al. Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result. *Lancet.* 2001;358(9285):861-865.
27. Gussekloo J, van Exel E, de Craen AJ, et al. Thyroid status, disability and cognitive function, and survival in old age. *JAMA.* 2004;292(21):2591-2599.
28. Heinze G, Schemper M. A solution to the problem of monotone likelihood in Cox regression. *Biometrics.* 2001;57(1):114-119.
29. Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med.* 1994;331(19):1249-1252.
30. Vittinghoff E, Glidden D, Shiboski S, McCulloch C. *Regression Methods in Biostatistics: Linear, Logistic, Survival, and Repeated Measures Models.* New York, NY: Springer-Verlag; 2005.
31. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315(7109):629-634.
32. Boekholdt SM, Titan SM, Wiersinga WM, et al. Initial thyroid status and cardiovascular risk factors. *Clin Endocrinol (Oxf).* 2010;72(3):404-410.
33. Asvold BO, Bjørø T, Nilsen TI, Gunnell D, Vatten LJ. Thyrotropin levels and risk of fatal coronary heart disease. *Arch Intern Med.* 2008;168(8):855-860.
34. Imaizumi M, Akahoshi M, Ichimaru S, et al. Risk for ischemic heart disease and all-cause mortality in subclinical hypothyroidism. *J Clin Endocrinol Metab.* 2004;89(7):3365-3370.
35. Sgarbi JA, Matsumura LK, Kasamatsu TS, et al. Subclinical thyroid dysfunctions are independent risk factors for mortality in a 7.5-year follow-up. *Eur J Endocrinol.* 2010;162(3):569-577.
36. Ladenson PW. Cardiovascular consequences of subclinical thyroid dysfunction. *Ann Intern Med.* 2008;148(11):880-881.
37. Cooper DS. Thyroid disease in the oldest old. *JAMA.* 2004;292(21):2651-2654.
38. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. *N Engl J Med.* 2001;344(7):501-509.
39. Klein I, Danzi S. Thyroid disease and the heart. *Circulation.* 2007;116(15):1725-1735.
40. Monzani F, Caraccio N, Kozáková M, et al. Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism. *J Clin Endocrinol Metab.* 2004;89(5):2099-2106.
41. Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community. *Clin Endocrinol (Oxf).* 1995;43(1):55-68.
42. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology. *JAMA.* 2000;283(15):2008-2012.
43. Razvi S, Ingole L, Keeka G, et al. The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function, and quality of life in subclinical hypothyroidism. *J Clin Endocrinol Metab.* 2007;92(5):1715-1723.
44. Fatourech V, Lankarani M, Schryver PG, et al. Factors influencing clinical decisions to initiate thyroxine therapy for patients with mildly increased serum thyrotropin (5.1-10.0 mIU/L). *Mayo Clin Proc.* 2003;78(5):554-560.
45. Cappola AR. Subclinical thyroid dysfunction and the heart. *J Clin Endocrinol Metab.* 2007;92(9):3404-3405.