Meta-analysis: Subclinical Thyroid Dysfunction and the Risk for Coronary Heart Disease and Mortality

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Background: Data on the association between subclinical thyroid dysfunction and coronary heart disease (CHD) and mortality are conflicting.

Purpose: To summarize prospective evidence about the relationship between subclinical thyroid dysfunction and CHD and mortality.

Data Sources: MEDLINE (1950 to January 2008) without language restrictions and reference lists of retrieved articles were searched.

Study Selection: Two reviewers screened and selected cohort studies that measured thyroid function and then followed persons prospectively to assess CHD or mortality.

Data Extraction: By using a standardized protocol and forms, 2 reviewers independently abstracted and assessed studies.

Data Synthesis: Ten of 12 identified studies involved population-based cohorts that included 14 449 participants. All 10 population-based cohort studies examined risks associated with subclinical hypothyroidism (2134 CHD events and 2822 deaths), whereas only 5 examined risks associated with subclinical hyperthyroidism (1392 CHD events and 1993 deaths). In a random-effects model, the relative risk (RR) for subclinical hypothyroidism for CHD was 1.20 (95% CI, 0.97 to 1.49; P for heterogeneity = 0.14; I^2 = 33.4%). Risk estimates were lower when higher-quality studies were pooled (RR, 1.02 to 1.08) and were higher among participants younger than 65 years (RR, 1.51 [CI, 1.09 to 2.09] for studies with mean participant age <65 years and 1.05 [CI, 0.90 to 1.22] for studies with mean participant age ≥65 years). The RR was 1.18 (CI, 0.98 to 1.42) for cardiovascular mortality and 1.12 (CI, 0.99 to 1.26) for total mortality. For subclinical hyperthyroidism, the RR was 1.21 (CI, 0.88 to 1.68) for CHD, 1.19 (CI, 0.81 to 1.76) for cardiovascular mortality, and 1.12 (CI, 0.89 to 1.42) for total mortality (P for heterogeneity >0.50; I^2 = 0% for all studies).

Limitations: Individual studies adjusted for different potential confounders, and 1 study provided only unadjusted data. Publication bias or selective reporting of outcomes could not be excluded.

Conclusion: Subclinical hypothyroidism and hyperthyroidism may be associated with a modest increased risk for CHD and mortality, with lower risk estimates when pooling higher-quality studies and larger CIs for subclinical hyperthyroidism.

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Subclinical thyroid dysfunction refers to patients who have an abnormal thyrotropin (thyroid-stimulating hormone [TSH]) level and a normal free thyroxine (T_4) level (1). The prevalence of subclinical hypothyroidism is about 4.3% in adults (0.7% for subclinical hyperthyroidism), and prevalence is higher in older adults and women (2–5). Controversy persists about whether screening and treating subclinical thyroid dysfunction is warranted (1, 5–7) because current evidence about the risks is limited (1, 5) and randomized, controlled trials on relevant clinical outcomes have not been done (5, 8).

Subclinical hypothyroidism has been associated with elevated cholesterol levels (9–11) and increased risk for atherosclerosis (12, 13). Yet, data on the relationship between subclinical hypothyroidism and coronary heart disease (CHD) events are conflicting (12, 14–17). In a previous meta-analysis (18), we found that subclinical hypothyroidism was associated with a 1.65-fold increased risk (CI, 1.28 to 2.12) for CHD. However, that meta-analysis included several cross-sectional and case–control studies and only 5 small prospective studies. Recently, 3 large prospective studies on this issue have been published (14, 16, 17), with somewhat inconsistent results. Because these new data include many additional CHD events, data are now sufficient to do a meta-analysis that includes only prospective studies, which provide greater validity. Data on the association between subclinical hypothyroidism and mortality are also conflicting (14, 17, 19, 20).

The consequences of subclinical hyperthyroidism have been less frequently studied than those of subclinical hypothyroidism. Subclinical hyperthyroidism has been associated with cardiovascular and total mortality (15), but with conflicting data (14, 17). Two of the 3 recent, large prospective studies (14, 17) also examined CHD and mortality in subclinical hyperthyroid participants. To summarize prospective evidence about the relationship between subclinical thyroid dysfunction and CHD and mortality, we did a systematic review of prospective cohort studies.

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Context

Is subclinical thyroid dysfunction associated with increased risk for coronary heart disease and mortality?

Contribution

This systematic review of 12 prospective cohort studies found that both subclinical hypothyroidism and hyperthyroidism were possibly associated with a small increased risk for coronary heart disease and mortality.

Caution

Data were uncertain. Confidence intervals around risk estimates were wide, particularly for those related to subclinical hyperthyroidism. Higher-quality studies showed lower estimates of risk than lower-quality studies.

Implication

Randomized trials testing the efficacy of thyroxine replacement and antithyroid medications for subclinical hypothyroidism and subclinical hyperthyroidism are needed.

—The Editors

METHODS

We followed a standardized protocol and conducted and reported this analysis according to the guidelines of the Meta-analysis Of Observational Studies in Epidemiology group (21).

Data Sources and Searches

We conducted a systematic literature search of MEDLINE for articles in any language on the association between subclinical thyroid dysfunction (both subclinical hypothyroidism and hyperthyroidism) and CHD or mortality (cardiovascular and total) published from 1950 to January 2008. To avoid missing any relevant study, we also searched the bibliographies of key articles in the field and those included in this review. We did our search on an Ovid (MEDLINE) server by using broadly defined Medical Subject Headings, such as *thyroid diseases, hypothyroidism, hyperthyroidism, thyroid hormones, thyrotropin, mortality, myocardial ischemia, survival*, and *cardiovascular diseases* and such keywords as *subclinical hypothyroidism, subclinical hyperthyroidism, subclinical dysthyroidism*, and *subclinical thyroid*, combined with the filter designed by knowledge information specialists from *BMJ* to select prospective studies (MEDLINE cohort-study filter) (22) but without their year limitation.

Study Selection

Two reviewers independently screened the abstracts and titles of the search results and eliminated articles only if they did not clearly study the association between subclinical thyroid dysfunction and CHD or mortality (cardiovascular or total) in a prospective design. The same 2 reviewers independently evaluated the remaining full-text articles for eligibility on the basis of a predefined set of eligibility criteria. Disagreements were resolved by consensus. We included only full-text, published, longitudinal cohort studies that measured thyroid function and followed persons prospectively, assessed CHD or mortality, and provided risk estimates or sufficient data to calculate risk estimates associated with subclinical thyroid dysfunction compared with normal thyroid function. Subclinical hypothyroidism was defined as elevated TSH levels and normal T_4 levels (1). Several reviews suggest a TSH upper limit cutoff of 4.5 to 5.0 mU/L (1, 5), but others suggest decreasing the upper limit of the TSH range to 2.5 to 3.0 mU/L (23, 24). In the absence of consensus, we did not prespecify a TSH cutoff value to define subclinical hypothyroidism and did a sensitivity analysis by limiting the analysis to studies with a TSH cutoff of 4.5 mU/L or greater (5). Because most adults with elevated TSH levels have subclinical and not overt hypothyroidism (2), we included 2 studies with participants who had elevated TSH levels without a T_4 measurement report (25, 26) and did a sensitivity analysis excluding those studies.

For subclinical hyperthyroidism, we did not specify a TSH cutoff value (in the absence of consensus), but all studies had a cutoff value close to 0.3 to 0.5 mU/L. We included 1 study with participants who had low TSH levels without a reported T_4 measurement (26) and did a sensitivity analysis excluding this study. For CHD, we considered myocardial infarction, angina, the acute coronary syndrome, revascularization (coronary artery surgery, percutaneous transluminal coronary angioplasty), and significant coronary stenosis (defined as ≥50%) (27). We also considered death due to CHD or cardiovascular disease and did a sensitivity analysis excluding studies that only included the latter. We assessed methods and criteria used for adjudication of those outcomes.

The agreement between the 2 reviewers was 99.5% for the first screen (titles and abstracts; $\kappa = 0.79$) and 100% for the full-text screen ($\kappa = 1.00$).

Data Extraction and Quality Assessment

Two reviewers independently abstracted data on participant characteristics, criteria used to define subclinical thyroid dysfunction, CHD and mortality data, and study results with adjustment factors by using a standardized data collection form. Discrepancies in data extraction between reviewers were resolved by consensus. We systematically assessed key indicators of study quality (28): methods of outcome adjudication and ascertainment that account for confounders and completeness of follow-up ascertainment. Similar to our previous meta-analysis (18), study populations were considered either a convenience or a population-based sample (defined as a random sample of the general population) (29). Methods of outcome adjudication were categorized as use of formal adjudication procedures and adjudication without knowledge of thyroid status. A for-

Table 1. **Population-Based Studies of Subclinical Thyroid Dysfunction and Risk for CHD and Mortality***

Study, Year (Reference)	Sample	Mean Age (Range or SD), *y*	Women, %	Follow-up	
				Initial	Duration
Subclinical hypothyroidism					
Population-based studies‡					
Aho et al., 1984 (25)	280 men from rural areas of eastern and southwestern Finland	64.5 (55–74)§	0	1974	5 y
Vanderpump et al., 1996 (30) (Whickham study)	478 adults from mixed urban and rural areas near Newcastle, United Kingdom**	46 (18–95)	55.3	1972–1974	20 y
Hak et al., 2000 (12) (Rotterdam study)	957 women living in a district in Rotterdam, the Netherlands	69 (>55)	100	1990–1993	4.6 y
Parle et al., 2001 (15)	1171 community-dwelling adults in Birmingham, United Kingdom	70.4 (>60)	57.2	1988–1989	8.2 y
Imaizumi et al., 2004 (20) (Nagasaki Adult Health Study)	999 atomic bomb survivors in Nagasaki, Japan	58 (10)	0	1984–1987	6 y
	2550 atomic bomb survivors in Nagasaki, Japan	58 (10)	60.8	1984–1987	10 y
	999 atomic bomb survivors in Nagasaki, Japan	58 (10)	0	1984–1987	6 y
Gussekloo et al., 2004 (19) (Leiden 85-plus Study)	558 adults living in 1 urban district in Leiden, the Netherlands	85	66	1997–1999	3.7 y
Rodondi et al., 2005 (16) (Health, Aging, and Body Composition Study)	2730 community-dwelling adults in areas surrounding Pittsburgh, Pennsylvania, and Memphis, Tennessee	74.7 (70–79)	51	NR	4 y
Walsh et al., 2005 (17) (Busselton Health Study)	1926 adults living in Busselton, Western Australia	49.8 (17–89)	49.6	1981	20 y
Cappola et al., 2006 (14) (Cardiovascular Health Study)	3233 community-dwelling adults in 4 U.S. communities: Washington County, Maryland; Allegheny County, Pennsylvania; Sacramento County, California; and Forsyth County, North Carolina	72.7 (≥65)	59.6	1989–1990	12.5 y
Bauer et al., 2007 (26) (Study of Osteoporotic Fractures)	487 community-dwelling women in 4 U.S. communities: Portland, Oregon; Minneapolis, Minnesota; Baltimore, Maryland; and the Monongahela Valley, Pennsylvania‖	71.7 (≥65)	100	1986–1988	11.9 y
Convenience sample					
Iervasi et al., 2007 (31)	3121 patients admitted to 1 cardiology department (Pisa, Italy), excluding those with ACS or severe illness	61.1 (60.7–61.5)	32.6	2000–2006	2.7 y
Subclinical hyperthyroidism					
Population-based studies‡					
Parle et al., 2001 (15)	1171 community-dwelling adults in Birmingham, United Kingdom	70.4 (>60)	57.2	1988–1989	8.2 y

mal adjudication procedure was defined as having clear criteria for the outcomes that were reviewed by experts for each potential case (29) (for example, specific electrocardiogram or cardiac enzyme modifications for CHD). We did not consider CHD adjudication based only on death certificates as a formal adjudication procedure. If an article did not clearly mention 1 of these criteria, we considered that it had not been done.

We contacted the authors of 7 studies (12, 14, 15, 19, 26, 30, 31) that met inclusion criteria but did not provide specific data on the associations between subclinical thyroid dysfunction and CHD or mortality. We obtained risk estimates and CIs for cardiovascular and total mortality from cohort studies in the United Kingdom (15) and the Netherlands (19), as well as specific data for CHD mortality from a cohort of cardiac patients in Italy (31). Authors of a cohort study that published data about the relationship between autoimmune thyroid disease and CHD (30) provided us with data specific to subclinical hypothyroidism that were available for a subgroup of the participants.

Table 1—**Continued**

TSH Cutoff Value, *mU/L* (Number of Participants with Abnormal TSH Level)	Repeated TSH Measurement	Thyroxine Measured	Exclusion of Thyroid Hormone/ Antithyroid Drug Recipients	Outcome (Euthyroid/Subclinical Hypothyroid or Hyperthyroid Participants), *n/n*	Relative Risk (95% CI)†
Based on TSH distribution (24)‖	No	NR	NR/NA	Cardiovascular mortality (34/4)	1.25 (0.49–3.24)¶
>6.0 (26)	Yes, after 20 y	Yes	NR/NA	MI, angina, CHD mortality (174/12)	1.20 (0.78–1.85)¶
>4.0 (107)	No	Yes	Yes/NA	Fatal and nonfatal MI (10/4)	2.50 (0.70–9.10)
>5.0 (69)	Yes, yearly if abnormal TSH	Yes	Yes/Yes	Total mortality (444/25)	0.9 (0.6–1.4)††
				Cardiovascular mortality (118/10)	1.4 (0.7–2.6)††
>5.0 (96)	No	Yes	Yes/NA	CHD mortality (3/2)	4.8 (0.8–29.3)
>5.0 (257)	No	Yes	Yes/NA	Total mortality (268/42)	1.2 (0.8–1.6)
>5.0 (96)	No	Yes	Yes/NA	Cardiovascular mortality (6/2)	2.4 (0.5–11.8)
>4.8 (30)	Yes, at 3 y	Yes	Yes/Yes	Total mortality (180/6)	0.55 (0.24–1.25)
				Cardiovascular mortality (75/2)	0.47 (0.11–1.90)
≥4.5 (338)	No	Yes	No (only in an SA)/NA	CHD defined as MI, angina, CABG, CHD mortality (298/36)	0.85 (0.58–1.26)
				Total mortality (283/41)	1.20 (0.83–1.74)
				Cardiovascular mortality (94/10)	0.74 (0.34–1.61)
≥10.0 (44)	No			CHD defined as MI, angina, CABG, CHD mortality (298/5)	0.96 (0.35–2.61)
				Total mortality (283/8)	2.05 (0.90–4.68)
				Cardiovascular mortality (94/3)	2.26 (0.54–9.45)
>4.0 (101)	No	Yes	NR/NR	CHD defined as MI, angina, CHD mortality‡‡ (229/33)	1.8 (1.2–2.7)
				Cardiovascular mortality (170/21)	1.5 (0.9–2.5)
≥10.0 (44)	No			CHD defined as MI, angina, CHD mortality‡‡ (229/10)	2.6 (1.3–5.3)
>4.5 (496)	No	Yes	Yes/Yes§§	CHD defined as fatal and nonfatal MI, angina, CABG (883/161)	1.07 (0.90–1.28)
				Total mortality (1170/233)	1.14 (0.98–1.32)
				Cardiovascular mortality (474/101)	1.16 (0.92–1.46)
>5.5 (36)	No	NR	NR/NR	Total mortality (118/12)	1.23 (0.55–2.74)
				Cardiovascular mortality (43/3)	0.92 (0.25–3.34)
4.5–10.0 (208)	Yes, within 3 mo to exclude transient dysfunction	Yes	Yes/Yes	Total mortality (140/27)	2.01 (1.33–3.04)
				CHD mortality (48/12)	2.58 (1.38–4.87)
<0.44 (76)	Yes, yearly if abnormal TSH	Yes	Yes/Yes	Total mortality (444/33)	1.2 (0.9–1.8)††
				Cardiovascular mortality (118/11)	1.6 (0.8–2.9)††

Continued on following page

Three studies provided us with specific numbers of outcomes in each thyroid group (12, 14, 26).

We used the most adjusted risk estimates available (the model containing the greatest number of covariates), unless a separate model further adjusted for thyroid antibodies, because thyroid autoimmunity has been hypothesized to be a mediator in the association between subclinical hypothyroidism and CHD (20). We did a sensitivity analysis without the studies that adjusted for cholesterol because high cholesterol might be on the causal pathway. When risk estimates and CIs were not provided but raw data were available (25, 30, 32), we calculated relative risks (RRs) and CIs by using the Woolf method (33–35).

Data Synthesis and Analysis

We first qualitatively synthesized data, paying particular attention to which definitions of subclinical thyroid

Table 1—**Continued**

Study, Year (Reference)	Sample	Mean Age (Range or SD), *y*	Women, %	Follow-up	
				Initial	Duration
Gussekloo et al., 2004 (19) (Leiden 85-plus Study)	558 adults living in 1 urban district in Leiden, the Netherlands	85	66.0	1997–1999	3.7 y
Walsh et al., 2005 (17) (Busselton Health Study)	1926 adults living in Busselton, Western Australia	49.8 (17–89)	49.6	1981	20 y
Cappola et al., 2006 (14) (Cardiovascular Health Study)	3233 community-dwelling adults in 4 U.S. communities: Washington County, Maryland; Allegheny County, Pennsylvania; Sacramento County, California; and Forsyth County, North Carolina	72.7 (≥65)	59.6	1989–1990	12.5 y
Bauer et al., 2007 (26) (Study of Osteoporotic Fractures) Convenience sample	487 community-dwelling women in 4 U.S. communities: Portland, Oregon; Minneapolis, Minnesota; Baltimore, Maryland; and the Monongahela Valley, Pennsylvania‖‖	71.7 (≥65)	100	1986–1988	11.9 y
Radácsi et al., 2003 (32)	93 patients with a history of stroke or hip replacement undergoing rehabilitation at a geriatric hospital in Hungary	77 (64–87)	64.5	NR	2 y
Iervasi et al., 2007 (31)	3121 patients admitted to 1 cardiology department (Pisa, Italy), excluding those with ACS or severe illness	61.1 (60.7–61.5)	32.6	2000–2006	2.7 y

* ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CHD = coronary heart disease; MI = myocardial infarction; NA = not applicable; NR = not reported; SA = sensitivity analysis; TSH = thyroid-stimulating hormone.
† Relative risks were estimated on the basis of hazard ratios in 8 studies (14–17, 19, 20, 26, 31).
‡ A population-based study was defined as a random sample of the general population.
§ The mean age for this population was not available in the article or from the authors and was assumed to be age 64.5 years.
‖ Elevated TSH was defined as a TSH level >2 SDs above the mean of the thyroid autoantibody–negative participants.
¶ Relative risks and CIs were calculated from raw data.
** Data specific to subclinical hypothyroidism, defined as elevated TSH levels, and the development of CHD were available from the authors only for a subgroup of the study.
†† Study authors provided relative risk for subclinical hypothyroidism after exclusion of 18 participants with low thyroxine levels and relative risk for subclinical hyperthyroidism after exclusion of 2 participants with high thyroxine levels.
‡‡ Coronary heart disease events were defined as death from CHD or hospital admission with a diagnosis of CHD (International Classification of Diseases, Ninth Revision, Clinical Modification, codes 410–414).
§§ This study also accounted for thyroid hormone use during follow-up, analyzing it as a time-dependant covariate.
‖‖ Nested sample of the overall cohort.

dysfunction were used and which outcomes were measured. To calculate summary estimates and CIs of the risk for subclinical thyroid dysfunction, we pooled both RRs and hazard ratios (HRs) by using random-effects models based on the variance model developed by DerSimonian and Laird (36). Analyses were repeated by using fixed-effects models for comparison. The presence of heterogeneity across studies was evaluated by using the *Q* statistic with a conservative *P* value of 0.10 (37). We also calculated the I^2 statistic, which describes the total variation across studies attributable to heterogeneity rather than chance; an I^2 value greater than 50% indicated at least moderate statistical heterogeneity (38). To explore sources of heterogeneity, we did several predefined sensitivity and subgroup analyses, all with a random-effects model. Given the recent findings of a possible protective effect of subclinical hypothyroidism in very elderly persons (19, 39), we conducted stratified analyses by mean age of the studied populations by using various cutoff values (age <65 years or ≥65 years, and age <60 years, 60 to 79.9 years, or ≥80 years). We also repeated the meta-analysis after limiting the analysis to multiply adjusted studies, studies with a TSH cutoff value of 4.5 mU/L or greater or 10.0 mU/L or greater (5), studies using formal adjudication procedures, and studies that excluded thyroid hormone or antithyroid drug recipients. Finally, we did an influence analysis to assess the effect of individual studies on the summary estimates (40, 41).

We used the Egger test (42) and funnel plots to help assess the possibility of publication bias. We conducted all statistical analyses by using STATA software, version 9.2 (Stata, College Station, Texas).

Role of the Funding Source

The Department of Ambulatory Care and Community Medicine and the Institute of Social and Preventive Medicine of the University of Lausanne, Lausanne, Switzerland, funded this study. The funding source had no role in defining questions, abstracting data, synthesizing results,

Table 1—Continued

TSH Cutoff Value, *mU/L* (Number of Participants with abnormal TSH Level)	Repeated TSH Measurement	Thyroxine Measured	Exclusion of Thyroid Hormone/ Antithyroid Drug Recipients	Outcome (Euthyroid/Subclinical Hypothyroid or Hyperthyroid Participants), *n*	Relative Risk (95% CI)†
<0.3 (17)	Yes, at 3 y	Yes	Yes/Yes	Total mortality (180/7) Cardiovascular mortality (75/3)	1.20 (0.59–2.69) 1.38 (0.43–4.39)
<0.4 (37)	No	Yes	NR/NR	CHD defined as MI, angina, CHD mortality ‡‡ (229/5) Cardiovascular mortality (170/3)	1.3 (0.6–3.3) 1.0 (0.2–4.3)
<0.45 (47)	No	Yes	Yes/Yes§§	CHD defined as fatal and nonfatal MI, angina, CABG (883/18) Total mortality (1170/24) Cardiovascular mortality (474/9)	1.04 (0.64–1.69) 1.08 (0.72–1.62) 0.94 (0.49–1.83)
≤0.5 (53)	No	NR	NR/NR	Total mortality (118/17) Cardiovascular mortality (43/7)	0.86 (0.39–1.87) 0.91 (0.28–2.95)
<0.5 (21)	Yes, at 2 y	Yes	NR/NR	Total mortality (18/10) Cardiovascular mortality (2/5)	1.69 (0.93–3.07)¶ 7.62 (1.59–36.40)¶
<0.3 (98)	Repeated within 3 mo to exclude transient dysfunction	Yes	Yes/Yes	Total mortality (140/9) CHD mortality (48/7)	1.22 (0.62–2.40) 2.67 (1.20–5.92)

preparing the manuscript, or deciding to submit the manuscript for publication.

RESULTS

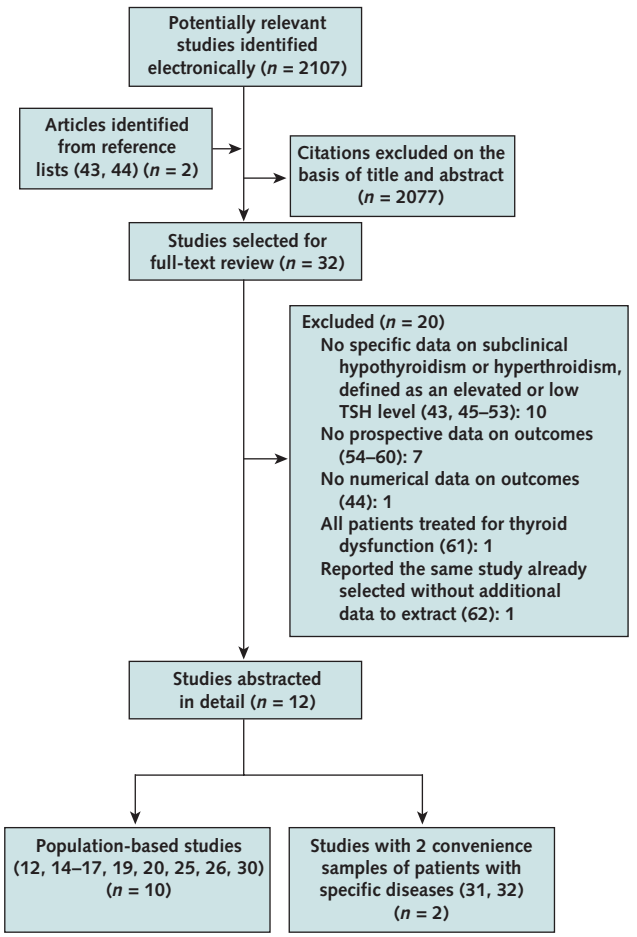
Study Selection

Of the 2109 reports identified, we excluded 2077 studies that were unrelated to the association between subclinical thyroid dysfunction and CHD or mortality and 20 after detailed evaluation. **Figure 1** shows details of the study selection. When similar data were published twice (19, 62), we included the original article with the most definitive and extractable form (19). Twelve prospective studies met eligibility criteria. Ten studies were population-based studies and included 14 449 community-living adults without substantive comorbid conditions. Two were convenience samples of patients with specific diseases: cardiac patients (31) or patients with a history of stroke or hip replacement (32). Given the clinical heterogeneity between these 2 types of studies, we pooled the 10 population-based studies as the core of this analysis and examined the addition of the 2 convenience samples in subsidiary analyses. All 10 of the population-based studies examined subclinical hypothyroidism, and 5 also examined subclinical hyperthyroidism.

Description and Quality of Studies

Table 1 shows the study characteristics and the effect of subclinical hypothyroidism and hyperthyroidism on the risk for CHD and cardiovascular and total mortality. Participants were mostly middle-aged or older men and women. Follow-up ranged from 2 to 20 years. All studies used standard assays for thyroid function (63), with TSH cutoff values of 4.0 to 6.0 mU/L for subclinical hypothyroidism and 0.3 to 0.5 mU/L for subclinical hyperthyroidism. Only the 2 convenience samples of patients were specifically designed to evaluate associations between thyroid function and CHD or mortality (31, 32). Three studies repeated assessments of thyroid function before the end of

Figure 1. **Study flow diagram.**



TSH = thyroid-stimulating hormone.

the follow-up (15, 19, 31), and 7 excluded persons treated with thyroid hormone.

Study quality was heterogeneous. Five studies reported formal adjudication procedures, and 8 adjudicated outcomes without knowledge of thyroid status (**Appendix Table 1**, available at www.annals.org). If an article did not clearly mention 1 of these characteristics, we considered it not to have been done. When reported, 5% or fewer participants in most studies were lost to follow-up. Only 4 studies adjusted for most cardiovascular risk factors, and several studies adjusted for only a few confounding factors.

Subclinical Hypothyroidism and CHD

Several studies suggested that subclinical hypothyroidism was associated with a small increased risk for CHD; only 1 of these (17) had statistically significant findings (**Figure 2**). In a random-effects model, the summary RR of CHD associated with subclinical hypothyroidism was 1.20 (CI, 0.97 to 1.49) for 2134 CHD events, with weak evidence of heterogeneity (P for heterogeneity = 0.14; I^2 = 33.4%) (**Table 2**). Studies that adjusted for cardiovascular risk factors yielded similar results. The summary RR was 1.02 for the 5 studies that used formal adjudication procedures and 1.08 for the 8 studies that adjudicated outcomes without knowledge of thyroid status. The 3 studies (14, 16, 19) that met most of our quality criteria (**Appendix Table 1**, available at www.annals.org)—all conducted in older adults—had point estimates less than or close to 1.0 (1.07 in the study by Cappola and colleagues [14]). In subgroup analysis by age, the summary RR was 1.51 for studies whose samples had mean age younger than 65 years and 1.05 for studies whose samples had a mean age 65 years or older. Compared with the overall random-effects model, these subgroup analyses had lower heterogeneity (P for heterogeneity = 0.32 to 0.42; I^2 = 0.0% to 15.4%). Using other age cutoff levels revealed a similar pattern.

Excluding 2 studies that did not report T_4 measurement (with the possible inclusion of some participants with overt hypothyroidism), those that included thyroid hormone recipients, or those that included cardiovascular death instead of CHD as outcomes yielded similar results (data not shown). The RR of the pooled estimates from the 2 studies that gave data for a TSH cutoff value of 10.0 mU/L or higher was 1.69 (CI, 0.64 to 4.45). Because data specific to subclinical hypothyroidism were available only for a subgroup in the study by Vanderpump and colleagues (30), we did a sensitivity analysis including all participants that showed a pooled RR of 1.18 (CI, 0.96 to 1.46).

Subclinical Hypothyroidism and Total and Cardiovascular Mortality

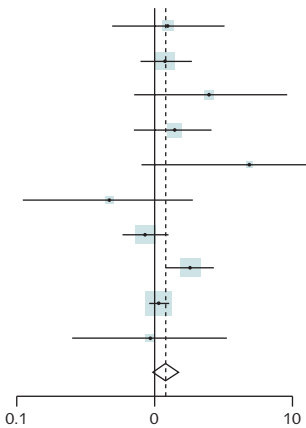
Several studies demonstrated a pattern of increased risk for total or cardiovascular mortality associated with subclinical hypothyroidism (**Figure 2**). For 2822 deaths, the summary RR was 1.12 (CI, 0.99 to 1.26) for total mortality and 1.18 (CI, 0.98 to 1.42; P for heterogeneity >0.50 for both; I^2 = 0%) for 1167 cardiovascular deaths. Most sensitivity analyses yielded similar results (**Appendix Tables 2** and **3**, available at www.annals.org). For cardiovascular mortality, pooling studies in which the mean age of participants was less than 65 years yielded an RR of 1.50; the RR was 1.12 if participants were 65 years or older. However, this analysis should be considered with caution because of the small number of studies.

Subclinical Hyperthyroidism and CHD

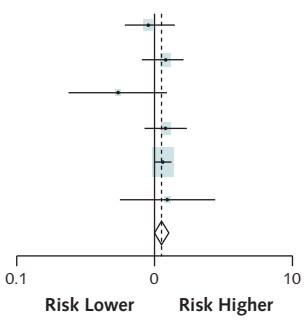
Several studies demonstrated a pattern of an increased risk for CHD associated with subclinical hyperthyroidism (**Figure 3**), with a summary RR of 1.21 (CI, 0.88 to 1.68; P for heterogeneity = 0.85; I^2 = 0%) for 1392 CHD events. Most sensitivity analyses yielded similar results (**Table 3**), except for lower point estimates when 2 studies with adjustment for most cardiovascular risk factors (RR, 1.10) and 3 studies with formal adjudication procedures (RR, 1.06) were pooled. We found no differences by mean age.

Figure 2. **Forest plots for subclinical hypothyroidism.**

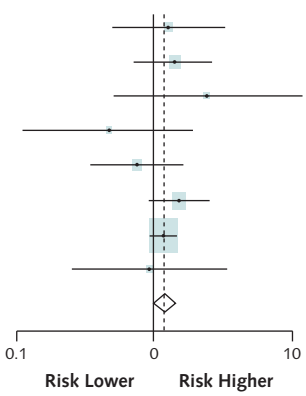
Study, Year (Reference)	Subclinical Hypothyroid Group		Euthyroid Group		Relative Risk (95% CI)	Weight, %
	CHD Events, *n*	Participants, *n*	CHD Events, *n*	Participants, *n*		
Coronary heart disease						
Aho et al., 1984 (25)	4	24	34	256	1.25 (0.49–3.24)	4.65
Vanderpump et al., 1996 (30)	12	26	174	452	1.20 (0.78–1.85)	15.06
Hak et al., 2000 (12)	4	107	10	850	2.50 (0.70–9.10)	2.68
Parle et al., 2001 (15)	10	76	118	1026	1.40 (0.70–2.60)	8.49
Imaizumi et al., 2004 (20)	2	257	3	2293	4.80 (0.80–29.30)	1.41
Gussekloo et al., 2004 (19)	2	30	75	472	0.47 (0.11–1.90)	2.20
Rodondi et al., 2005 (16)	36	338	298	2392	0.85 (0.58–1.26)	17.00
Walsh et al., 2005 (17)	33	101	229	1752	1.80 (1.20–2.70)	16.19
Cappola et al., 2006 (14)	161	496	883	2639	1.07 (0.90–1.28)	29.69
Bauer et al., 2007 (26)	3	36	43	398	0.92 (0.25–3.34)	2.63
Total (I^2 = 33.4%; P = 0.140)	267	1491	1867	12 530	1.20 (0.97–1.49)	100.00



Study, Year (Reference)	Subclinical Hypothyroid Group		Euthyroid Group		Relative Risk (95% CI)	Weight, %
	Deaths, *n*	Participants, *n*	Deaths, *n*	Participants, *n*		
Total mortality						
Parle et al., 2001 (15)	25	76	444	1026	0.90 (0.60–1.40)	8.04
Imaizumi et al., 2004 (20)	42	257	268	2293	1.20 (0.80–1.60)	12.01
Gussekloo et al., 2004 (19)	6	30	180	472	0.55 (0.24–1.25)	2.12
Rodondi et al., 2005 (16)	41	338	283	2392	1.20 (0.83–1.74)	10.53
Cappola et al., 2006 (14)	233	496	1170	2639	1.14 (0.98–1.32)	65.06
Bauer et al., 2007 (26)	12	36	118	398	1.23 (0.55–2.74)	2.24
Total (I^2 = 0.0%; P = 0.51)	359	1233	2463	9220	1.12 (0.99–1.26)	100.00



Study, Year (Reference)	Subclinical Hypothyroid Group		Euthyroid Group		Relative Risk (95% CI)	Weight, %
	CV Deaths, *n*	Participants, *n*	CV Deaths, *n*	Participants, *n*		
Cardiovascular mortality						
Aho et al., 1984 (25)	4	24	34	256	1.25 (0.49–3.24)	3.84
Parle et al., 2001 (15)	10	76	118	1026	1.40 (0.70–2.60)	7.96
Imaizumi et al., 2004 (20)	2	257	6	2293	2.40 (0.50–11.80)	1.37
Gussekloo et al., 2004 (19)	2	30	75	472	0.47 (0.11–1.90)	1.69
Rodondi et al., 2005 (16)	10	338	94	2392	0.74 (0.34–1.61)	5.67
Walsh et al., 2005 (17)	21	101	170	1752	1.50 (0.90–2.50)	13.14
Cappola et al., 2006 (14)	101	496	474	2639	1.16 (0.92–1.46)	64.29
Bauer et al., 2007 (26)	3	36	43	398	0.92 (0.25–3.34)	2.04
Total (I^2 = 0.0%; P = 0.65)	153	1358	1014	11 228	1.18 (0.98–1.42)	100.00



The diamonds represent relative risks and the horizontal lines represent 95% CIs of the effect of subclinical hypothyroidism. CHD = coronary heart disease; CV = cardiovascular.

Subclinical Hyperthyroidism and Total and Cardiovascular Mortality

The RR for total mortality was 1.12 (CI, 0.89 to 1.42) for 1993 deaths and 1.19 (CI, 0.81 to 1.76) for 913 cardiovascular deaths (P for heterogeneity >0.80 for both; $I^2 = 0\%$) (**Figure 3**). Most sensitivity analysis yielded similar results (**Appendix Tables 4** and **5**, available at www.annals.org), except for an RR of 0.95 for cardiovascular mortality (when 2 studies adjusted for most cardiovascular risk factors were pooled) and 1.01 for 3 studies with formal adjudication procedures.

Additional Studies Not Included in the Primary Analyses

For both subclinical hypothyroidism and hyperthyroidism, addition of the convenience samples of patients with specific diseases (31, 32) increased the point estimates for CHD and mortality (summary RRs, 1.18 to 1.55 [**Tables 2** and **3**; **Appendix Tables 2**, **3**, **4**, and **5**, available at www.annals.org]). These summary RRs reached or were close to statistical significance but had increased statistical heterogeneity for all associations.

Publication Bias Evaluation

We found no evidence of publication bias, either with visual assessment of funnel plots (data not shown) or with the Egger test (P >0.30 for all associations). Because small negative studies are most subject to publication bias and some might be missing, we excluded studies with fewer than 500 participants and obtained similar estimates for all associations. Influence analysis indicated that the exclusion of single studies did not substantially alter any estimates (data not shown).

Discussion

In the meta-analysis of 10 population-based prospective cohort studies, we found that subclinical thyroid dysfunction was associated with a pattern of modest increased risk for CHD and mortality (summary RRs, 1.12 to 1.21). Estimates about subclinical hyperthyroidism, which were derived from only 5 studies, had wider CIs than estimates for subclinical hypothyroidism. In general, we found lower risk estimates (RR, 1.01 to 1.21), when we pooled higher-quality studies, such as those that used formal adjudication procedures for outcomes although the upper bound of the CIs for these estimates was still consistent with overall summary RRs of increased risk. The relationship between subclinical hypothyroidism and CHD seemed to differ among studies that involved middle-aged versus elderly participants, with studies whose samples had a mean age younger than 65 years showing increased risk for CHD. Subclinical hypothyroid participants with a TSH 10.0 mU/L or greater might also have an increased CHD risk, but only 2 studies reported such stratified data. Risk estimates were higher when the 2 convenience samples of patients with specific diseases were added.

For the association between subclinical hypothyroid-

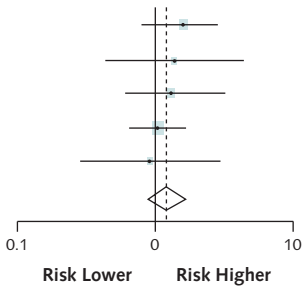
Table 2. **Stratified Analysis of the Association of Subclinical Hypothyroidism with Risk for CHD***

Characteristic	Summary Relative Risk (95% CI)†	Studies, *n*
Eligible study model		
Random effects	1.20 (0.97–1.49)	10
Fixed effects	1.14 (1.00–1.30)	10
Study quality		
Formal CHD or cardiovascular mortality rate adjudication procedures	1.02 (0.86–1.22)	5
Adjudication without knowledge of thyroid status	1.08 (0.90–1.31)	8
Stratified by mean age		
<65 y	1.51 (1.09–2.09)	4
≥65 y	1.05 (0.90–1.22)	6
<60 y	1.58 (1.02–2.43)	3
60–79.9 y	1.06 (0.91–1.24)	6
≥80 y	0.47 (0.11–1.90)	1
Adjustments		
Adjusted analyses or matching	1.21 (0.93–1.58)	9
Adjusted for cardiovascular risk factors	1.22 (0.86–1.73)	4
Definition of subclinical hypothyroidism		
TSH level ≥4.5 mU/L	1.06 (0.91–1.25)	7
TSH level ≥10.0 mU/L	1.69 (0.64–4.45)	2
Particular population: elderly participants excluded (19)	1.22 (0.99–1.52)	9
Subsidiary analysis: addition of a convenience sample of cardiac patients (31)	1.31 (1.02–1.67)‡	11

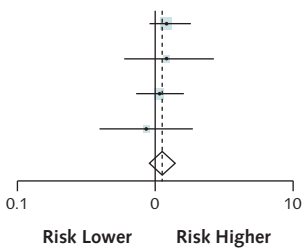
* CHD = coronary heart disease; TSH = thyroid-stimulating hormone.
† Relative risk from meta-analysis using random-effects model.
‡ Addition of the convenience sample of cardiac patients increased overall statistical heterogeneity (P for heterogeneity = 0.03; $I^2 = 49.0\%$).

Figure 3. **Forest plots for subclinical hyperthyroidism.**

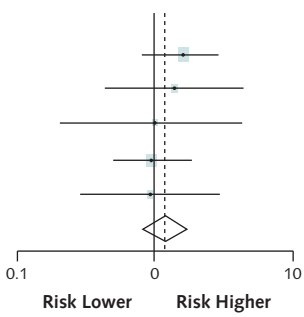
Study, Year (Reference)	Subclinical Hyperthyroid Group		Euthyroid Group		Relative Risk (95% CI)	Weight, %
	CHD Events, *n*	Participants, *n*	CHD Events, *n*	Participants, *n*		
Coronary heart disease						
Parle et al., 2001 (15)	11	69	118	1026	1.60 (0.80–2.90)	25.41
Gussekloo et al., 2004 (19)	3	17	75	472	1.38 (0.43–4.39)	7.81
Walsh et al., 2005 (17)	5	37	229	1752	1.30 (0.60–3.30)	14.50
Cappola et al., 2006 (14)	18	47	883	2639	1.04 (0.64–1.69)	44.69
Bauer et al., 2007 (26)	7	53	43	398	0.91 (0.28–2.95)	7.60
Total (I^2 = 0.0%; P = 0.85)	44	223	1348	6287	1.21 (0.88–1.68)	100.00



Study, Year (Reference)	Subclinical Hyperthyroid Group		Euthyroid Group		Relative Risk (95% CI)	Weight, %
	Deaths, *n*	Participants, *n*	Deaths, *n*	Participants, *n*		
Total mortality						
Parle et al., 2001 (15)	33	69	444	1026	1.20 (0.90–1.80)	46.84
Gussekloo et al., 2004 (19)	7	17	180	472	1.20 (0.59–2.69)	9.78
Cappola et al., 2006 (14)	24	47	1170	2639	1.08 (0.72–1.62)	34.22
Bauer et al., 2007 (26)	17	53	118	398	0.86 (0.39–1.87)	9.16
Total (I^2 = 0.0%; P = 0.85)	81	186	1912	4535	1.12 (0.89–1.42)	100.00



Study, Year (Reference)	Subclinical Hyperthyroid Group		Euthyroid Group		Relative Risk (95% CI)	Weight, %
	CV Deaths, *n*	Participants, *n*	CV Deaths, *n*	Participants, *n*		
Cardiovascular mortality						
Parle et al., 2001 (15)	11	69	118	1026	1.60 (0.80–2.90)	36.53
Gussekloo et al., 2004 (19)	3	17	75	472	1.38 (0.43–4.39)	11.22
Walsh et al., 2005 (17)	3	37	170	1752	1.00 (0.20–4.30)	6.44
Cappola et al., 2006 (14)	9	47	474	2639	0.94 (0.49–1.83)	34.89
Bauer et al., 2007 (26)	7	53	43	398	0.91 (0.28–2.95)	10.93
Total (I^2 = 0.0%; P = 0.81)	33	223	880	6287	1.19 (0.81–1.76)	100.00



The diamonds represent relative risks and the horizontal lines represent 95% CIs of the effect of subclinical hyperthyroidism. CHD = coronary heart disease; CV = cardiovascular.

ism and CHD, several population-based studies yielded conflicting results. Two individual prospective studies found a statistically significant association between subclinical hypothyroidism and CHD: the Busselton Health Study (HR, 1.8) (17) and a sample of cardiac patients (HR, 2.58) (31). However, 2 large prospective cohort studies of older adults found no increased risk for CHD (14, 16). These 2 studies adjusted their results for most cardiovascular risk factors and met most of our quality criteria, whereas the 2 studies with substantial associations (17, 31) did not formally adjudicate cardiovascular outcomes or report whether adjudication was done without knowledge of thyroid status. A meta-analysis pooled only 3 recent studies (14, 16, 17) and obtained a summary RR of 1.19 (CI, 1.02 to 1.38) (64), driven in part by the use of the unadjusted RR of 2.5 from the Busselton Health Study (adjusted HR, 1.8) (65). In our previous meta-analysis (18), we found a statistically significant association between subclinical hypothyroidism and CHD (summary odds ratio, 1.65 [CI, 1.28 to 2.12]), but that analysis included 3 case–control and 6 cross-sectional studies. When our previous meta-analysis of subclinical hypothyroidism and CHD was lim-

Table 3. **Stratified Analysis of the Association of Subclinical Hyperthyroidism with Risk for CHD***

Characteristic	Summary Relative Risk (95% CI)†	Studies, *n*
Eligible study models		
Random effects	1.21 (0.88–1.68)	5
Fixed effects	1.21 (0.88–1.68)	5
Study quality		
Formal CHD or cardiovascular mortality rate adjudication procedures	1.06 (0.70–1.61)	3
Adjudication without knowledge of thyroid status	1.20 (0.84–1.70)	4
Stratified by mean age		
<65 y	1.3 (0.6–3.3)	1
≥65 y	1.20 (0.84–1.70)	4
<60 y	1.3 (0.6–3.3)	1
60–79.9 y	1.18 (0.82–1.71)	3
≥80 y	1.38 (0.43–4.39)	1
Adjustments		
Adjusted analyses or matching	1.21 (0.88–1.68)	5
Adjusted for cardiovascular risk factors	1.10 (0.72–1.68)	2
Particular population: elderly participants excluded (19)	1.20 (0.86–1.68)	4
Subsidiary analysis: addition of 2 convenience samples (31, 32)	1.54 (1.04–2.28)‡	7

* CHD = coronary heart disease.
† Relative risk from meta-analysis using random-effects model.
‡ Addition of the 2 convenience samples increased overall statistical heterogeneity (P for heterogeneity = 0.17; I^2 = 34.2%).

ited to the 5 older prospective cohort studies (12, 15, 20, 25, 30) that were of lower quality than the more recent ones, the summary RR was 1.42 (CI, 0.91 to 2.21).

Our analyses showed a pattern of higher mortality rates in participants with subclinical hypothyroidism, consistent with 2 previous meta-analyses that found slightly higher risks (summary RRs, 1.25 and 1.21 [66] and 1.12 and 1.28 [64] for total and cardiovascular mortality, respectively). However, these older meta-analyses included only 4 studies with mortality outcomes (14, 16, 17, 20) and had some limitations, such as data extraction errors (64, 65) and lack of assessment of statistical heterogeneity or sensitivity analyses (66). Our results might not apply to all ages, because 1 study found an even lower risk for total mortality (HR, 0.55) in adults age 85 years with subclinical hypothyroidism than in euthyroid participants (19).

Similar to a previous meta-analysis (66), we found a pattern of modestly increased risk for CHD and mortality associated with subclinical hyperthyroidism, with wider CIs than those for subclinical hypothyroidism, given the more limited data, and lower risk estimates when higher-quality studies were pooled. Further large studies are needed to better assess these risks. The higher risks found in the 2 convenience samples of patients with specific diseases, particularly for subclinical hyperthyroidism, increase the likelihood that subclinical thyroid dysfunction associated with other diseases might be a different, potentially more harmful entity than subclinical thyroid dysfunction among healthier individuals or that sick patients might be less tolerant to abnormal levels of TSH. We previously found that associations between subclinical hypothyroidism and heart failure were stronger for recurrent than for incident events (16). However, these differences are based on only 2 prospective cohorts of patients with specific diseases and should be confirmed in other studies.

We found weak evidence for statistical heterogeneity among individual study findings, and age explained part of the heterogeneity for the association between subclinical hypothyroidism and CHD, with an increased risk for CHD only in cohorts with a younger mean age. These potential age differences should be interpreted with caution, given the possibility of ecological fallacy without individual patient data (28). One cross-sectional study did subgroup analyses by age and found that the risk for CHD associated with subclinical hypothyroidism was higher in younger participants (67); however, no prospective study presented stratified analyses by age. Although this finding should be confirmed by stratified analyses in future prospective cohort studies with a wide age range, potential explanations for these age differences might be competing mortality among older adults (for example, due to cancer) or more competing risk factors for CHD among older adults (for example, age or sex). If the risk for CHD with subclinical hypothyroidism was mainly mediated by increased cholesterol levels, it might weaken with age because levels of total and low-density lipoprotein cholesterol are strong cardiovascular risk factors in middle-age but not older adults (68). Other potential explanations could be related to thyroid physiology in older adults (decreased thyroid hormone action at the tissue level, decreased thy-

roid hormone metabolism) (39). High TSH levels in elderly persons might also be a compensatory mechanism for other perturbations, whereas in younger adults it is caused by thyroid dysfunction.

Our study has several limitations. First, a meta-analysis of observational studies should be interpreted with caution (69), even though it can provide useful information when only data from observational studies are available (21). To our knowledge, no randomized, controlled trial has studied the benefits of treating adults with subclinical thyroid dysfunction with regard to CHD or mortality (5,8). We found only weak evidence for statistical heterogeneity among studies, but some clinical heterogeneity with slightly different TSH cutoff levels (4.0 to 6.0 mU/L for subclinical hypothyroidism and 0.3 to 0.5 mU/L for subclinical hyperthyroidism), varying CHD definitions, or different confounding factors included for adjustment. We could not assess the risk for specific CHD outcomes, such as MI or "hard" CHD (MI, coronary death) outcomes, because such subgroup analysis was lacking in most original studies. However, sensitivity analyses pooling more homogeneous studies yielded similar risk estimates, although such estimates were lower when higher-quality studies were pooled. Alternative explanations for observed results are bias in the selection of included studies, bias and quality problems in the original studies, publication bias, heterogeneity, and confounding (21).

To limit bias in the selection of included studies, we used broad inclusion criteria for studies that provided quantitative data on the risk for CHD or mortality associated with subclinical thyroid dysfunction and then did sensitivity analyses according to differences between the studies and methodological study quality, as recommended (21, 70). We could not exclude all participants with inadequately treated overt thyroid dysfunction or nonthyroidal illness (71) because these subgroup data were lacking in the original studies. Subgroup analyses should be interpreted with caution given the limited number of studies. Although our graphical and statistical analyses showed that publication bias was unlikely, it cannot be excluded because the capacity to detect publication bias is reduced when meta-analyses are based on a limited number of studies (42, 72). Selective reporting of the outcomes in the cohorts cannot be excluded, either.

In summary, our data suggest that subclinical thyroid dysfunction might represent a potentially modifiable—albeit modest—risk factor for CHD and mortality. Assuming that treatment is effective, given the high prevalence of thyroid disease even a small increase in CHD or mortality rates among persons with subclinical dysfunction (such as the 10% to 20% increased RR in our study) would have public health implications. From a health policy perspective, it would be premature to recommend screening for thyroid dysfunction in the general population. Given the pattern of modestly increased risk for CHD and mortality associated with subclinical thyroid dysfunction, lower risk estimates in higher-quality studies, and the remaining uncertainty, treatment of subclinical thyroid dysfunction with CHD as an end point should be studied in randomized, placebo-controlled trials to assess the efficacy of T_4 replacement or antithyroid medications before current recommendations are updated (1, 5).

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Appendix Table 2. **Stratified Analysis of the Association of Subclinical Hypothyroidism with Risk for Total Mortality***

Characteristic	Summary Relative Risk (95% CI)†	Studies, *n*
Eligible study model		
Random effects	1.12 (0.99–1.26)	6
Fixed effects	1.12 (0.99–1.26)	6
Study quality		
<5% of participants lost to follow-up‡	1.13 (0.99–1.28)	4
Stratified by mean age§		
<65 y	1.20 (0.80–1.60)	1
≥65 y	1.10 (0.96–1.26)	5
<60 y	1.20 (0.80–1.60)	1
60–79.9 y	1.12 (0.99–1.28)	4
≥80 y	0.55 (0.24–1.25)	1
Adjustments		
Adjusted analyses or matching	1.12 (0.99–1.26)	6
Adjusted for cardiovascular risk factors	1.15 (1.00–1.32)	2
Definition of subclinical hypothyroidism		
TSH level ≥4.5 mU/L	1.12 (0.99–1.26)	6
TSH level ≥10.0 mU/L	2.05 (0.90–4.68)	1
Particular population: elderly participants excluded (19)	1.13 (1.00–1.28)	5
Subsidiary analysis: addition of a convenience sample of cardiac patients (31)	1.18 (0.96–1.44)‖	7

* TSH = thyroid-stimulating hormone.
† Relative risk from meta-analysis using random-effects model.
‡ A cutoff of <5% of participants lost to follow-up was considered appropriate on the basis of retention data of other large cohort studies (73).
§ The number of studies in each age category is small, with only 1 study in the younger age groups.
‖ Addition of the convenience sample of cardiac patients increased overall statistical heterogeneity (P for heterogeneity = 0.08; I^2 = 47.6%).

Appendix Table 3. Stratified Analysis of the Association of Subclinical Hypothyroidism with Risk for Cardiovascular Mortality*

Characteristic	Summary Relative Risk (95% CI)†	Studies, *n*
Eligible study model		
Random effects	1.18 (0.98–1.42)	8
Fixed effects	1.18 (0.98–1.42)	8
Study quality		
Formal cardiovascular mortality rate adjudication procedures	1.09 (0.88–1.35)	4
Adjudication without knowledge of thyroid status	1.13 (0.92–1.39)	6
Stratified by mean age		
<65 y	1.50 (0.97–2.30)	3
≥65 y	1.12 (0.91–1.37)	5
<60 y	1.57 (0.96–2.55)	2
60–79.9 y	1.14 (0.93–1.40)	5
≥80 y	0.47 (0.11–1.90)	1
Adjustments		
Adjusted analyses or matching	1.18 (0.98–1.42)	8
Adjusted for cardiovascular risk factors	1.17 (0.92–1.49)	3
Definition of subclinical hypothyroidism		
TSH level ≥4.5 mU/L	1.13 (0.92–1.39)	6
TSH level ≥10.0 mU/L	2.26 (0.54–9.45)	1
Particular population: elderly participants excluded (19)	1.20 (0.99–1.44)	7
Subsidiary analysis: addition of a convenience sample of cardiac patients (31)	1.29 (1.01–1.67)‡	9

* TSH = thyroid-stimulating hormone.
† Relative risk from meta-analysis by using random-effects model.
‡ Addition of the convenience sample of cardiac patients increased overall statistical heterogeneity (P for heterogeneity = 0.24; I^2 = 23.4%).

Appendix Table 4. Stratified Analysis of the Association of Subclinical Hyperthyroidism with Risk for Total Mortality*

Characteristics	Summary Relative Risk (95% CI)†	Studies, *n*
Eligible study model		
Random effects	1.12 (0.89–1.42)	4
Fixed effects	1.12 (0.89–1.42)	4
Study quality		
<5% of participants lost to follow-up‡	1.12 (0.87–1.43)	3
Adjustments		
Adjusted analyses or matching	1.12 (0.89–1.42)	4
Adjusted for cardiovascular risk factors	1.08 (0.72–1.62)	1
Particular population: elderly participants excluded (19)	1.12 (0.87–1.43)	3
Subsidiary analysis: addition of 2 convenience samples (31, 32)	1.19 (0.97–1.47)§	6

* Stratified analyses by mean age are not reported for this relationship because of the limited number of studies.
† Relative risk from meta-analysis using random-effects model.
‡ A cutoff of <5% of participants lost to follow-up was considered appropriate on the basis of retention data of other large cohort studies (73).
§ Addition of the 2 convenience samples did not increase overall statistical heterogeneity (P for heterogeneity = 0.82; I^2 = 0%).

Appendix Table 5. **Stratified Analysis of the Association of Subclinical Hyperthyroidism with Risk for Cardiovascular Mortality***

Characteristics	Summary Relative Risk (95% CI)†	Studies, *n*
Eligible study model		
Random effects	1.19 (0.81–1.76)	5
Fixed effects	1.19 (0.81–1.76)	5
Study quality		
Formal cardiovascular mortality rate adjudication procedures	1.01 (0.60–1.69)	3
Adjudication without knowledge of thyroid status	1.21 (0.81–1.81)	4
Adjustments		
Adjusted analyses or matching	1.19 (0.81–1.76)	5
Adjusted for cardiovascular risk factors	0.95 (0.52–1.74)	2
Particular population: elderly participants excluded (19)	1.17 (0.77–1.77)	4
Subsidiary analysis: addition of 2 convenience samples (31, 32)	1.55 (0.99–2.43)‡	7

* Stratified analyses by mean age are not reported for this relationship because of the limited number of studies.
† Relative risk from meta-analysis using random-effects model.
‡ Addition of the 2 convenience samples increased overall statistical heterogeneity (P for heterogeneity = 0.17; I^2 = 34.0%).

Appendix Table 1. **Quality Assessment of Included Studies***

Study, Year (Reference)	Formal Adjudication Procedures for CHD†	Methods for CHD Ascertainment	Formal Adjudication Procedures for Cardiovascular Mortality Rate†	Methods for Cardiovascular Mortality Rate Ascertainment	Adjudication without Knowledge of Thyroid Status	Lost to Follow-up, %	Adjustments	Report of Missing Covariates
Population-based studies								
Aho et al., 1984 (25)	NA	NA	No	NR	No	NR	Age- and locality-matched, unadjusted	NR
Vanderpump et al., 1996 (30) (Whickham study)	No	Self-reported history of angina or MI confirmed by general practitioners or hospital records	NA	Death certificates, postmortem reports, hospital or general practitioners' reports, ECG during the final illness coded (36%)	Yes	3	Unadjusted	NR
Hak et al., 2000 (12) (Rotterdam study)	Yes	Reports from general practitioners and hospital records	NA	NA	Yes	1.8	Age, BMI, total cholesterol, HDL, BP, and smoking	BMI, 8; BP, 5; HDL, 4; smoking: 18
Parle et al., 2001 (15)	NA	NA	No	Death certificates; causes of death coded with ICD-9	Yes	0.1	Age and sex	NR
Imaizumi et al., 2004 (20) (Nagasaki Adult Health Study)	NA	NA	No	Death certificates; causes of death coded with ICD-9	Yes	0 for mortality	Age, sex, and smoking	NR
Gussekloo et al., 2004 (19) (Leiden 85-plus Study)	NA	NA	Yes	Mortality information from general practitioners with a standardized questionnaire: causes of death coded by 2 experts with ICD-10	Yes	12.5	Sex and education	NR
Rodondi et al., 2005 (16) (Health, Aging, and Body Composition Study)	Yes	Interview, hospital records, and other support documents reviewed by a panel of clinicians	Yes	Hospital records, death certificates, and other support documents reviewed by a panel of clinicians	Yes	NR	Age, sex, race, smoking, diabetes, prevalent CVD, poor or fair health, BP, total cholesterol, creatinine, education, income, thyroid hormone, and ACE inhibitor use	NR
Walsh et al., 2005 (17) (Busselton Health Study)	No	Hospital records: diagnoses coded with ICD-9 and ICD-10	No	Registrar General's list of deaths: coded with ICD-9 and ICD-10	No	5	Age, sex, BMI, smoking, diabetes, total cholesterol, triglycerides, BP, hypertensive therapy, exercise, and thyroid disease	NR
Cappola et al., 2006 (14) (Cardiovascular Health Study)	Yes	Interview, hospital records reviewed by experts	Yes	Medical records, death certificates, autopsy reports, and coroners' reports reviewed by experts	Yes	0 for mortality	Age, sex, prevalent CVD, thyroid medication, race, smoking, diabetes, LDL cholesterol, lipid-lowering drugs, hypertension, BMI, and CRP	NR
Bauer et al., 2007 (26) (Study of Osteoporotic Fractures)	NA	NA	Yes	Hospital records, death certificates reviewed by a physician-investigator and coded with ICD-9	Yes	1	Age, weight, thyroid hormone or estrogen use, history of hyperthyroidism	NR
Convenience samples								
Radácsi et al., 2003 (32)	NA	NA	No	Death information obtained from general practitioners	No	NR	Unadjusted	NR
Iervasi et al., 2007 (31)	NA	NA	No	Death certificates, hospital records, general practitioner and patient interviews (if living)	No	0 for mortality	Age, sex, ischemic and nonischemic heart disease	NR

* If an article did not clearly mention 1 of these characteristics, we considered it not to have been done. ACE = angiotensin-converting enzyme; BMI = body mass index; BP = blood pressure; CHD = coronary heart disease; CRP = C-reactive protein; CVD = cardiovascular disease; ECG = electrocardiography; HDL = high-density lipoprotein; ICD = International Classification of Diseases; LDL = low-density lipoprotein; MI = myocardial infarction; NA = not applicable (because the outcome was not examined in the study); NR = not reported.
† A formal adjudication procedure was defined as having clear criteria for the outcome that were reviewed by experts for each potential case.