The American Journal of Medicine (2006) 119, 541-551

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THE AMERICAN JOURNAL of MEDICINE®

REVIEW

AJM Theme AJM Theme Issue: Cardiology

Subclinical Hypothyroidism and the Risk of Coronary Heart Disease: A Meta-Analysis

Nicolas Rodondi, MD, MAS,[a,b] Drahomir Aujesky, MD, MS,[c,d] Eric Vittinghoff, PhD,[a] Jacques Cornuz, MD, MPH,[b] Douglas C. Bauer, MD[a,e]

[a]Department of Epidemiology and Biostatistics, University of California, San Francisco, [b]University Institute of Social and Preventive Medicine, Department of Community Medicine and Public Health, University of Lausanne, Lausanne, Switzerland, [c]Division of General Internal Medicine, Department of Medicine, University of Pittsburgh, Pittsburgh, Pa, [d]Department of Medicine, University of Lausanne, Lausanne, Switzerland, [e]Division of General Internal Medicine, Department of Medicine, University of California, San Francisco

ABSTRACT

PURPOSE: Subclinical hypothyroidism has been associated with elevated cholesterol and increased risk for atherosclerosis, but data on the risk of coronary heart disease (CHD) are conflicting. We performed a systematic review to determine whether subclinical hypothyroidism is associated with CHD in adults.

METHODS: We searched MEDLINE from 1966 to April 2005, and the bibliographies of key articles to identify studies that provided risk estimates for CHD or cardiovascular mortality associated with subclinical hypothyroidism. Two authors independently reviewed each potential study for eligibility, assessed methodologic quality, and extracted the data.

RESULTS: We identified 14 observational studies that met eligibility criteria. Subclinical hypothyroidism increased the risk of CHD (summary odds ratio [OR]: 1.65, 95% confidence interval [CI], 1.28-2.12). The summary OR for CHD was 1.81 (CI, 1.38-2.39) in 9 studies adjusted or matched for demographic characteristics, and 2.38 (CI, 1.53-3.69) after pooling the studies that adjusted for most cardiovascular risk factors. Sensitivity analyses including only population-based studies and those with formal outcome adjudication procedures yielded similar results. Subgroup analyses by type of study design showed a similar trend, but lower risk, in the 5 prospective cohort studies (OR 1.42, CI, 0.91-2.21), compared with the case-control and cross-sectional studies (OR 1.72, CI, 1.25-2.38).

CONCLUSION: Our systematic review indicates that subclinical hypothyroidism is associated with an increased risk of CHD. Clinical trials are needed to assess whether thyroxine replacement reduces the risk of CHD in subjects with subclinical hypothyroidism.

KEYWORDS: Subclinical hypothyroidism; Coronary disease; Meta-analysis.

Subclinical hypothyroidism refers to subjects who have an elevated thyroid-stimulating hormone (thyrotropin, TSH) level and a normal free thyroxine (T4) level.[1] Subclinical hypothyroidism is common, with an estimated prevalence in the US adult population of 4.3% in a recent analysis of the Third National Health and Nutrition Examination Survey.[2] The prevalence of subclinical hypothyroidism increases with age and is approximately 10% in women aged more than 60 years and somewhat lower in men.[2-4]

Subclinical hypothyroidism may increase the risk of coronary heart disease (CHD) by adversely affecting cardiovascular risk factors. Despite some conflicting results,[5] many studies[6-8] have found that subjects with subclinical hypothyroidism have higher total cholesterol and low-density lipoprotein/cholesterol levels than euthyroid subjects. A cross-sectional study showed that subjects with subclinical hypothyroidism have increased C-reactive protein values.[9] Subclinical hypothyroidism also has been associated with increased risk for atherosclerosis.[10-12]

Nicolas Rodondi was supported by a grant from the Swiss National Foundation (PBLAB-102353).

Requests for reprints should be addressed to Nicolas Rodondi, MD, MAS, Department of Community Medicine and Public Health, University of Lausanne, Bugnon 44, 1011 Lausanne, Switzerland.

E-mail address: Nicolas.Rodondi@hospvd.ch

0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2005.09.028

Data on the risk of CHD in subjects with subclinical hypothyroidism are conflicting.[4,13] Three of the 5 prospective studies included less than 40 CHD events each,[11,14,15] and thus had low power to detect an association between subclinical hypothyroidism and CHD. Many studies are cross-sectional[11,16-18] or case-control,[14,19,20] and some discrepancies may result from study design. Whereas 1 randomized controlled trial has shown benefits of treatment with thyroxine replacement on intima-media thickness,[10] a surrogate cardiovascular marker, none have assessed the impact of thyroxine replacement on clinical CHD in subjects with subclinical hypothyroidism.[4]

Qualitative reviews of the literature regarding the association of subclinical hypothyroidism and cardiovascular disease are available[21,22] but were not focused on CHD, and no quantitative summary analysis has been published. To determine whether subclinical hypothyroidism is associated with an increased risk for CHD, we performed a systematic review of observational studies that examined the relationship between subclinical hypothyroidism and the risk of CHD.

CLINICAL SIGNIFICANCE

- Our systematic review suggests that subclinical hypothyroidism is associated with an increased risk of coronary heart disease.
- Coronary heart disease is among the most life-threatening conditions that have been associated with subclinical hypothyroidism.
- Controversy persists regarding screening and treatment of subclinical hypothyroidism.

METHODS

Meta-analyses of observational studies present particular challenges because of inherent biases and differences in study designs.[23] We therefore conducted and reported this analysis according to the guidelines of the Meta-analysis of Observational Studies in Epidemiology Group.[24]

Data Sources

We conducted a systematic literature search of English, French, and German language articles on the association between subclinical hypothyroidism and CHD published between January 1966 and April 2005 in MEDLINE. We also searched the bibliographies of key articles in the field and those included in this review. To avoid missing any relevant study in our MEDLINE search, we used broadly defined medical subject heading terms: thyroid diseases, hypothyroidism, thyroid hormones, thyrotropin, coronary disease, myocardial ischemia, myocardial infarction, and keyword: subclinical hypothyroidism.

Study Selection

Two reviewers (NR, DA) independently screened the abstracts and titles of the search results, and articles were eliminated only if they did not study the association between thyroid disease and CHD. The same 2 reviewers independently evaluated studies for eligibility on the basis of a predefined set of eligibility criteria. We included studies that assessed the risk of CHD or cardiovascular mortality in subjects with subclinical hypothyroidism, compared with those with normal thyroid function, and provided risk estimates or sufficient data to calculate risk estimates. Subclinical hypothyroidism was defined as an elevated TSH and a normal T4.[1] Several reviews suggest a TSH upper limit cutoff of 4.5 to 5.0 mU/L,[1,4] but some authors suggest that the upper limit of the TSH range should be reduced to 2.5 to 3.0 mU/L,[25-27] based on a higher rate of progression to overt hypothyroidism and a higher prevalence of antithyroid antibodies than in euthyroid subjects.[28] In the absence of any consensus, we did not pre-specify a TSH cutoff to define subclinical hypothyroidism, but performed a sensitivity analysis after limiting the analysis to studies with a TSH cutoff of 4.5 mU/L or greater.[4] Three small studies included subjects with an elevated TSH, but did not report a T4 measurement.[14,20] We decided to include them and then to perform a sensitivity analysis excluding these 3 studies because some subjects may have overt hypothyroidism. For CHD, we considered myocardial infarction, angina, acute coronary syndrome, revascularization (coronary artery surgery, percutaneous transluminal coronary angiography), significant coronary stenosis ($\geq$50%),[29] and death caused by CHD or cardiovascular disease.

The 2 reviewers agreed on the inclusion/exclusion status of 93% of the studies reviewed. Disagreements were resolved by consensus.

Data Extraction

From each study that met our eligibility criteria, 2 reviewers (NR, DA) independently abstracted information about study designs (prospective cohort, cross-sectional, case-control study), subject characteristics, criteria used to define subclinical hypothyroidism, types of CHD recorded, and study results (effect estimates, factors included in the adjustments, or matching procedures) using a standardized data-collection form. Discrepancies in data extraction between reviewers were resolved by consensus. Because quality scoring is controversial in meta-analyses of observational studies,[24] we systematically assessed key indicators of study quality:[30] population studied (convenience sample vs population-based, defined as a random sample of the general population[31]) and method of outcome adjudication (use of formal adjudication procedures, adjudication without knowledge of thyroid status). A formal adjudication procedure was defined as having clear criteria for the outcome that were reviewed by experts for each potential case.[31] We did not consider CHD adjudication based only on death certificates

as a formal adjudication procedure. If an article did not clearly mention one of these criteria, we considered that it has not been done.

Because 3 studies met inclusion criteria, but did not provide specific data on the association between subclinical hypothyroidism and CHD, we contacted the authors. We obtained risk estimates and confidence intervals (CIs) specific to cardiovascular death from a cohort study in the United Kingdom,[32] and crude data for CHD from a study in Denmark.[33] The prospective cohort of the Whickham study published the relationship between autoimmune thyroid disease and CHD;[34] we obtained data specific to subclinical hypothyroidism from the authors who were available for a subgroup of the study, but we performed a sensitivity analysis including all subjects. For 2 studies that used several definitions for CHD,[17,20] we included the most specific and closest to our definition of CHD mentioned above.

We used the most adjusted risk estimates available and 95% CI, which was the model containing the greatest number of covariates, except if a separate model was further adjusted for thyroid antibodies, because thyroid autoimmunity has been hypothesized to be a mediator in the association between subclinical hypothyroidism and CHD.[15] We reported hazard ratios of 2 studies[15,32] as odds ratios (ORs), because they are good approximation of one another when the outcomes are rare[35] (1% and 11% of CHD events, respectively, in these 2 studies). When risk estimates and CI were not provided but raw data were available (9 studies), we calculated ORs from published crude data.

Statistical Analyses

We calculated summary estimates and 95% CI of the risk of subclinical hypothyroidism using random-effects models and the general variance-based method.[36] Analyses were repeated using a fixed-effects model for comparison. To assess heterogeneity between the studies, we performed a test for homogeneity using a chi-square test with a conservative P value of .10.[37] To explore sources of heterogeneity and determine the effect of differences in study methodology, we performed several predefined sensitivity and subgroup analyses. We repeated the meta-analysis by types of study design and used meta-regression analysis to establish the effect of study design, similar to previous meta-analyses.[38] We also repeated the meta-analysis after limiting the analysis to population-based studies, multiply adjusted studies, studies that reported T4 measurement, studies with a TSH cutoff of 4.5 mU/L or greater,[4] and studies using formal adjudication procedures. We also performed sensitivity analyses limiting our analyses to studies that did not exclude thyroid hormone users, because a similar approach was used in 2 major studies on the risk of subclinical thyroid disease.[39,40] We also performed a sensitivity analysis excluding studies that included overall cardiovascular death instead of CHD death. Three studies reported both cross-sectional and prospective results; we initially included both results for these 3 studies,[11,15,17,34] because different CHD events were included in each analysis. In 2 of these cross-sectional analyses, subclinical hypothyroidism was associated with an increased risk for CHD.[11,15] Thus we performed sensitivity analyses excluding either the prospective or the cross-sectional parts of these 2 studies.

Publication bias, the nonpublication of small studies with negative results, represents a particular threat to the validity of meta-analysis.[24] We used rank correlation tests and funnel plots to test for the presence of publication bias.[31,41] We conducted the statistical analyses using STATA 8.2 software (StataCorp, College Station, Tex).

RESULTS

Study Selection

Of the 753 reports initially identified, we excluded 719 studies that were unrelated to the association between thyroid disease and CHD (Appendix). Of the 34 articles selected for detailed evaluation, 9 studies did not assess the risk of CHD in subjects with subclinical hypothyroidism. Five studies did not provide specific data on subclinical hypothyroidism defined as an elevated TSH.[42-46] Two studies did not provide risk estimates and CI or the information necessary to calculate them from the report.[47,48] Two had no euthyroid control group.[49,50] We excluded 1 small study because of evidence that the analysis was done incorrectly.[51] When similar data were published twice,[18,52] we included the article with the most definitive and extractable form.[18] Fourteen observational studies met eligibility criteria.

Study Characteristics

Table 1 shows the study characteristics and the effect of subclinical hypothyroidism on the risk of CHD for all 14 studies included in our analysis. Most studies included subjects of both genders with a wide range of age. The TSH cutoff to define subclinical hypothyroidism ranged from 2.8 to 6.0 mU/L. All but 3 small studies also reported a T4 measurement.

Assessment of Study Quality

Most studies were population-based (Table 2). Approximately half of the studies reported formal adjudication procedures and an adjudication without knowledge of thyroid status. These 2 criteria were fulfilled in the same studies, except for one.[32] If an article did not clearly mention one of these characteristics, we considered that it has not been done, which may underestimate the reported characteristics.

Data Synthesis

Most studies demonstrated a trend toward an increased risk of CHD in subjects with subclinical hypothyroidism compared with euthyroid subjects, but these findings reached statistical significance only in 4 studies (Figure 1). One case-control study that included only 9 participants with subclinical hypothyroidism found subclinical hypothyroidism to be associated with a lower risk for CHD.[14] By using a random-effects model, the summary OR of CHD in subjects with subclinical hypothyroidism was 1.65 (95% CI,

Table 1 Description and Results of Included Studies of the Effect of Subclinical Hypothyroidism on the Risk of Coronary Heart Disease

First Author, Year	Population (No. of Subjects)	Subclinical hypothyroidism: TSH Cutoff (No. of Subjects)	Subclinical hypothyroidism: T4 Measured?	Exclusion of Thyroid Hormone Users?	CHD (No. of Subjects)/ Type of CHD	OR* (95% CI)	Adjustments
Prospective cohort studies:							
Aho, 1984[14] (East-West series)	Men aged 55-74 y (280)	Based on TSH distribution† (24)	NR/NA	NR/NA	Cardiovascular death (38)	1.31 (0.37-4.23)‡	Age and locality matched, unadjusted
Hak, 2000[11] (Rotterdam study)	Women aged >55 y (1036)	>4.0 mU/L (124)	Yes	Yes	MI (16)	2.50 (0.70-9.10)	Age, BMI, total cholesterol, HDL, blood pressure, smoking status
Imaizumi, 2004[15]	Men with a mean age of 58 y (999)	>5.0 mU/L (96)	Yes	Yes	CHD death (10)	4.8 (0.8-29.3)	Age, smoking status
Parle, 2001[32]	Men and women aged >60 y (1120)	>5.0 mU/L (94)	Yes	Yes	Cardiovascular death (128)	1.08 (0.56-2.09)	Age, sex
Vanderpump, 1996[34] (Whickham study)	Men and women aged 18-95 y (478)§	>6.0 mU/L (26)	Yes	NR/NA	MI, angina, CHD death (186)	1.37 (0.56-3.27)‡	Unadjusted
Cross-sectional studies:							
Hak, 2000[11] (Rotterdam study)	Women aged >55 y (994)	>4.0 mU/L (124)	Yes	Yes	MI (79)	2.30 (1.30-4.20)	Age, BMI, total cholesterol, HDL, blood pressure, smoking status
Imaizumi, 2004[15]	Men and women with a mean age of 58.5 y (2550)	>5.0 mU/L (257)	Yes	Yes	MI, angina (38)	2.5 (1.1-5.4)	Age, sex, BMI, total cholesterol, HDL, blood pressure, diabetes, smoking status, erythrocyte sedimentation rate
Kvetny, 2004 [33]	Men and women aged 20-69 y (1212)	>2.8 mU/L (249)	Yes	Yes	MI, angina (119)	1.35 (0.84-2.12)‡	Unadjusted
Lindeman, 2003[18] (New Mexico Elder Health Survey)	Men and women aged >65 y (755)	>4.6 mU/L (112)	Yes	No	MI, angina, CABG (213)	1.02 (0.63-1.62)‡	Unadjusted
Mya, 2002[16]	Men and women with a mean age of 75 y (249)	>4.7 mU/L (18)	Yes	Yes	MI, angina, revascularization (48)	6.35 (2.08-19.63)‡	Unadjusted
Tunbridge, 1977[17] (Whickham study)	Men and women aged >18 y (2592)	>6.0 mU/L (132)	Yes	NR/NA	MI, angina (156)	1.45 (0.69-2.77)‡	Unadjusted
Case-control studies							
Aho, 1984[14]	Men and women aged <65 y (194)	Based on TSH distribution† (9)	NR/NA	NR/NA	MI (97)	0.27 (0.03-1.48)‡	Age and sex matched, unadjusted

Table 1 Continued

First Author, Year	Population (No. of Subjects)	Subclinical hypothyroidism: TSH Cutoff (No. of Subjects)	Subclinical hypothyroidism: T4 Measured?	Exclusion of Thyroid Hormone Users?	CHD (No. of Subjects)/ Type of CHD	OR* (95% CI)	Adjustments
Miura, 1996[19]	Men and women with a mean age of 60 y (200)	>3.5 mU/L (23)	Yes	NR/NA	Coronary stenosis >75% in ≥1 major vessel (97)	2.17 (0.81-6.21)‡	Age, sex, and BMI matched, unadjusted
Tieche, 1981[20]	Men and women with a mean age of 59 y (352)	≥4.0 mU/L (121)	NR/NA	NR/NA	MI, angina (137)	1.77 (1.10-2.84)‡	Age and sex matched, unadjusted

BMI = body mass index; CABG = coronary artery surgery; CHD = coronary heart disease; CI = 95% confidence intervals; HDL = high-density lipoprotein; NR/NA = not reported or not available; MI = myocardial infarction; OR = odds ratio; TSH = thyroid-stimulating hormone.

*OR was estimated by the hazard ratio in 2 studies.[15,32]

†Elevated TSH was defined as a TSH >2 standard deviations above the mean of the thyroid autoantibody-negative subjects.

‡OR and CI were calculated from raw data.

§Data specific to subclinical hypothyroidism, defined as an elevated TSH, and the development of CHD were available only for a subgroup of the study from the authors.

1.28-2.12) compared with euthyroid subjects (Table 3). A fixed-effects model yielded similar results (OR 1.59, CI, 1.31-1.93). We found weak evidence for heterogeneity among individual study findings (P for heterogeneity = .12). Most of the heterogeneity resulted from a single relatively small cross-sectional study.[16] The omission of this study from the meta-analysis substantially reduced the heterogeneity (P for heterogeneity .38) and slightly decreased the summary OR (1.53, CI, 1.24-1.88).

Sensitivity and Subgroup Analysis

In studies with either statistical adjustment or matching cases with controls, the summary OR for CHD in subjects with subclinical hypothyroidism was 1.81 (95% CI, 1.38-2.39), and 2.38 (95% CI, 1.53-3.69) after pooling the 3 studies that adjusted for most cardiovascular risk factors. Sensitivity analyses including only studies with a TSH cutoff of 4.5 mU/L or greater, studies that excluded thyroid hormone users, population-based studies, and studies with formal adjudication procedures or adjudication without knowledge of thyroid status, or excluding studies that included cases with acute myocardial infarction or cardiovascular death instead of CHD, death yielded similar results. Excluding 3 small studies that did not report T4 measurement, and thus may have included some subjects with overt hypothyroidism, yielded similar results.

Subgroup analyses by type of study design showed a similar trend, but a lower risk, in the 5 prospective cohort studies (OR 1.42, CI, 0.91-2.21) compared with the summary estimate for case-control and cross-sectional studies (OR 1.72, CI, 1.25-2.38). Meta-regression analysis indicated that there was little evidence that the association differed by study design (P = .63). Excluding either the prospective or the cross-sectional parts of 2 studies that showed a significant cross-sectional association between subclinical hypothyroidism and CHD events[11,15] yielded an OR of 1.59 (CI, 1.22-2.07) and 1.52 (CI, 1.15-2.00), respectively. Because the data specific to subclinical hypothyroidism were available only for a subgroup of the prospective Whickham study, we performed a sensitivity analysis including all subjects,[34] and obtained a pooled OR of 1.54 (CI, 1.21-1.96).

Publication Bias Evaluation

The correlation between the effect size and the sample size of the studies was weak and not statistically significant (rank correlation test: r = −0.20, P = .16). The funnel plot suggested that there was little publication bias (Figure 2), although the small number of studies made it difficult to interpret. Because some small negative studies that are most subject to publication bias might be missing, we excluded studies with less than 500 participants and obtained similar summary OR (1.53, CI, 1.15-2.04) of CHD in subjects with subclinical hypothyroidism.

Table 2 Quality Assessment of Included Studies of the Effect of Subclinical Hypothyroidism on the Risk of Coronary Heart Disease*

First Author, Year	Population Studied	Formal Adjudication Procedures for CHD†	CHD Adjudication without Knowledge of Thyroid Status
Prospective cohort studies:			
Aho, 1984[14] (East-West series)	Population-based,‡ 2 regions (Finland)	No	No
Hak, 2000[11] (Rotterdam study)	Population-based,‡ 1 district (Holland)	Yes	Yes
Imaizumi, 2004[15]	Population-based,‡ 1 town (Japan)	Yes	Yes
Parle, 2001[32]	Population-based,‡ local sample (United Kingdom)	No	Yes
Vanderpump, 1996[34] (Whickham study)	Population-based,‡ 1 town (United Kingdom)	Yes	Yes
Cross-sectional studies:			
Hak, 2000[11] (Rotterdam study)	Population-based,‡ 1 district (Holland)	Yes	Yes
Imaizumi, 2004[15]	Population-based,‡ 1 town (Japan)	Yes	Yes
Kvetny, 2004[33]	Primary care center (Denmark)	No	No
Lindeman, 2003[18] (New Mexico Elder Health Survey)	Population-based,‡ 1 county (United States)	No	No
Mya, 2002[16]	Nursing home residents (United States)	No	No
Tunbridge, 1977[17] (Whickham study)	Population-based,‡ 1 town (United Kingdom)	No	No
Case-control studies			
Aho, 1984[14]	Hospital series (Finland)	No	No
Miura, 1996[19]	Inpatients (Japan)	No	No
Tieche, 1981[20]	Inpatients (Switzerland)	Yes	Yes

CHD = coronary heart disease.
*If an article did not clearly mention one of these characteristics, we considered that it has not been done.
†A formal adjudication procedure was defined as having clear criteria for the outcome that were reviewed by experts for each potential case.[31]
‡A population-based study was defined as a random sample of the general population.[31]

DISCUSSION

On the basis of the findings of this meta-analysis, we found that subclinical hypothyroidism was significantly associated with an increased risk of CHD. The pooled estimate of all eligible observational studies was consistent with a 1.6 odds of CHD in subjects with subclinical hypothyroidism compared with euthyroid subjects. Most studies showed a trend toward an increased risk of CHD, but only 4 reached statistical significance. We found no evidence that the risk of CHD in subjects with subclinical hypothyroidism was limited to unadjusted studies, or studies with lower methodologic quality. Subgroup analyses by type of study design showed a similar trend, but lower risk, in the 5 prospective cohort studies compared with the case-control and cross-sectional studies.

Previous studies on the risk of CHD in subjects with subclinical hypothyroidism yielded conflicting results.[4,13] By pooling the data of these individual studies, we analyzed a total of 1362 CHD outcomes and approximately 10,540 subjects, increasing our power to detect an association and reducing the probability of false-negative results.[53] However, the lower risk found in the 5 prospective cohort studies, compared with the case-control and cross-sectional studies, is of concern. Case-control and cross-sectional studies are more susceptible to bias, particularly selection bias for case-control studies, or effect-cause when the outcome influences the predictor.[31] Bias cannot be excluded, but the 2 cross-sectional studies that fulfilled all our quality criteria showed a statistically significant association between subclinical hypothyroidism and CHD.[11,15] Regarding effect-cause, it is possible that acute myocardial infarction included in 2 of the case-control studies[14,20] may have increased TSH levels rather than vice versa, but excluding these 2 studies yielded similar results. The lack of statistical association in the prospective cohort studies, despite a similar trend toward a higher CHD risk, may represent inadequate power to detect an association. Three of 5 prospective studies included fewer than 40 CHD events each.[11,14,15] Because the diagnoses of CHD were based on death certificates in 3 prospective studies,[14,15,32] and on retrospective data after 20 years of follow-up in 1 study,[34] misclassification of the outcome without objective documentation also might have diluted the association between subclinical hypothyroidism and CHD.

Our study did not elucidate the mechanisms by which subclinical hypothyroidism may increase CHD risk. Adjustment for traditional cardiovascular risk factors, including high total cholesterol that is associated with subclinical hypothyroidism,[6-8] did not decrease this risk, but only 3 studies adjusted for most cardiovascular risk factors.[11,15] The published studies did not provide sufficient data to assess whether the risk of CHD associated with subclinical hypothyroidism was mediated or independent of total cholesterol and low-density lipoprotein/cholesterol levels. It has been postulated that the CHD risk associated with subclinical hypothyroidism might also be mediated by a hyper-

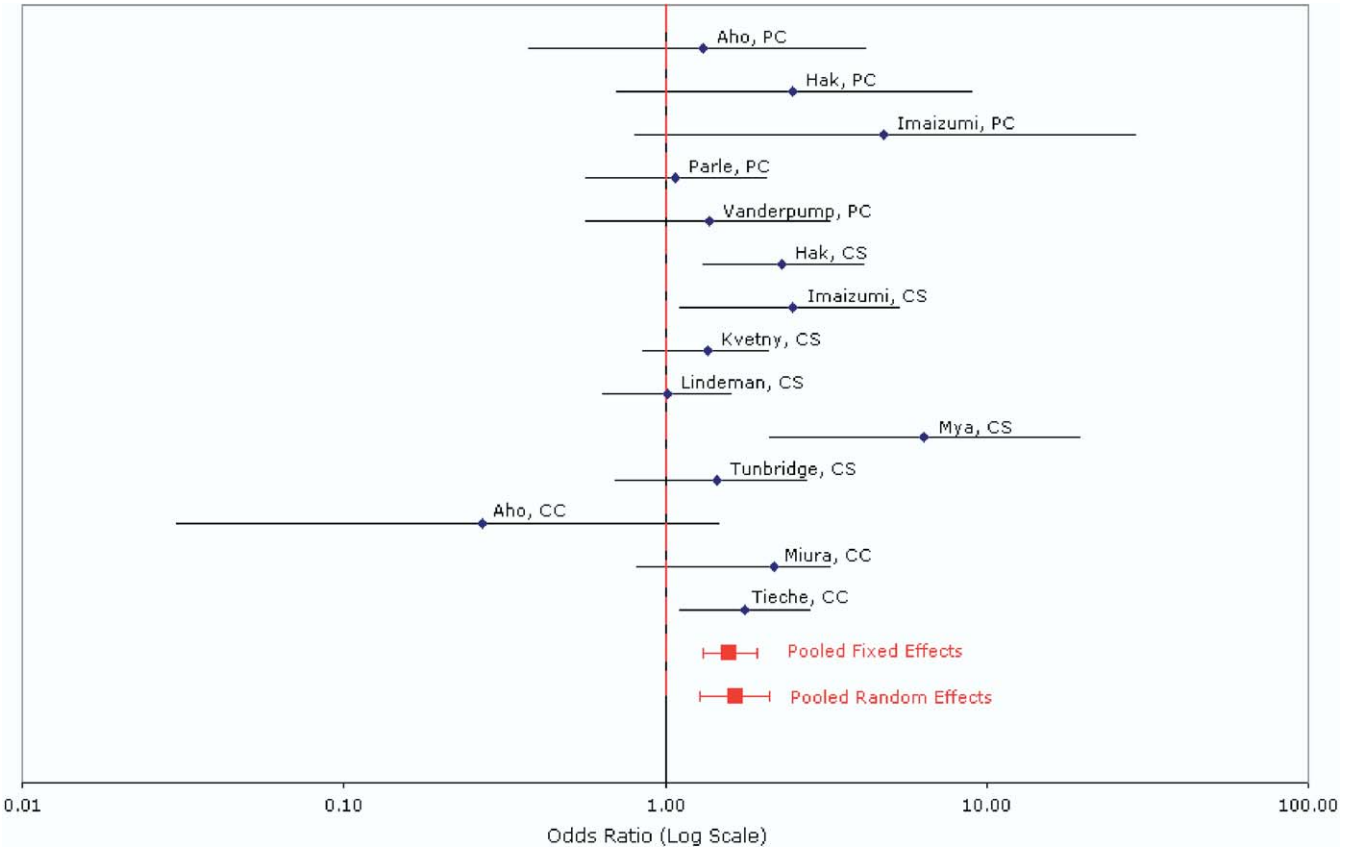

Figure 1 Forest plot of odds ratios (ORs) of coronary heart disease (CHD) associated with subclinical hypothyroidism. ORs (diamonds) and 95% confidence intervals (CIs) (horizontal lines) of the effect of subclinical hypothyroidism on the risk of CHD. CC = case-control study; CS = cross-sectional study; PC = prospective cohort study.

coagulable state[54] or some emerging cardiovascular risk factors, such as C-reactive protein and lipoprotein A.[9,55] Future studies should consider these possibilities.

Randomized studies have not assessed the impact of thyroxine replacement on clinical cardiac endpoints,[4] but 1 study assessed the effect of thyroxine replacement on intima-media thickness. Intima-media thickness is a marker of subclinical atherosclerosis that is associated with an increased risk of myocardial infarction, even after adjusting for traditional cardiovascular risk factors.[56] This study, a randomized, placebo-controlled trial, found a significant 10% decrease in mean intima-media thickness (0.09 mm, 95% CI: 0.06-0.11) after 6 months of thyroxine replacement, with a decrease of similar magnitude in the 18 participants with TSH less than 10 mU/L.[10] However, this trial included few subjects (n = 45) and did not assess clinical cardiac endpoints. Other mechanisms than increased atherosclerosis might also explain the CHD risk associated with subclinical hypothyroidism, such as a hypercoagulable state.[54] Clinical trials should confirm that this decrease in a surrogate marker of subclinical cardiovascular disease also is related to a decrease in the risk of CHD in subjects with subclinical hypothyroidism.

Should we screen and treat subclinical hypothyroidism? Controversy persists as to whether screening and treatment of subclinical hypothyroidism are warranted[1,4,13,57] because current evidence about the benefits and the risks is limited.[1,4] This is an important issue because many subjects with subclinical hypothyroidism are currently treated in clinical practice.[58] If substantial risk of CHD associated with subclinical hypothyroidism is true, it would be an important argument to screen for this disease. The risk of CHD is among the most life-threatening condition that has been associated with subclinical hypothyroidism.[4] However, approximately 20% of patients are currently overtreated by thyroxine replacement with an increased risk of subclinical hyperthyroidism that has been associated with atrial fibrillation, reduced bone mineral density, and cardiac dysfunction.[4] Moreover, thyroxine replacement might have adverse effects on mortality in the elderly,[59] because a recent study found that adults aged 85 years or older with subclinical hypothyroidism had lower total mortality than euthyroid adults.[40] The current evidence on the risk of subclinical hypothyroidism is also limited by the small number of published studies and the lack of well-done prospective cohorts with a large number of CHD events. Randomized, controlled trials with CHD as the endpoint should be performed to assess the efficacy of thyroxine replacement to reduce the risk of CHD in subjects with subclinical hypothyroidism and to prove the causal relationship.

Table 3 Sensitivity and Subgroup Analysis of the Effect of Subclinical Hypothyroidism on the Risk of Coronary Heart Disease

Study Characteristics	Summary OR*	95% CI	*P* for Heterogeneity	No. of Studies
Sensitivity analysis				
All eligible studies				
Random effects	1.65	1.28-2.12	.12	14
Fixed effects	1.59	1.31-1.93	.12	14
Adjustments				
Adjusted analyses or matching	1.81	1.38-2.39	.40	9
Adjusted for cardiovascular risk factors	2.38	1.53-3.69	.98	3
Definition of subclinical hypothyroidism				
TSH $\geq$ 4.5 mU/L	1.70	1.08-2.68	.04	7
Measurement of T4 reported	1.71	1.28-2.30	.09	11
Exclusion of thyroid hormone users reported	2.06	1.36-3.14	.08	7
Definition of CHD				
Without studies that included cardiovascular death†	1.75	1.32-2.32	.10	12
Without studies that included cases with acute MI[14,20]	1.68	1.27-2.21	.13	12
Characteristics of study quality				
Formal CHD adjudication procedures	2.03	1.50-2.74	.78	6
CHD adjudication without knowledge of thyroid status	1.82	1.39-2.39	.49	7
Population-based study	1.54	1.16-2.04	.31	9
Subgroup analysis				
Study design				
Prospective cohort studies	1.42	0.91-2.21	.52	5
Cross-sectional and case-control studies	1.72	1.25-2.38	.05	9

OR = odds ratio; CI = 95% confidence intervals; CHD = coronary heart disease; TSH = thyroid-stimulating hormone; MI = myocardial infarction.
*ORs from meta-analysis using random-effects model.
†No specific data on CHD death, but data on overall cardiovascular death.[14,32]

Our analysis has several limitations. First, all data were obtained from observational studies. Meta-analyses of observational studies should be interpreted with caution[60] but can provide useful information when only data from observational studies are available.[24] Alternative explanations for observed results are bias in the selection of included studies,

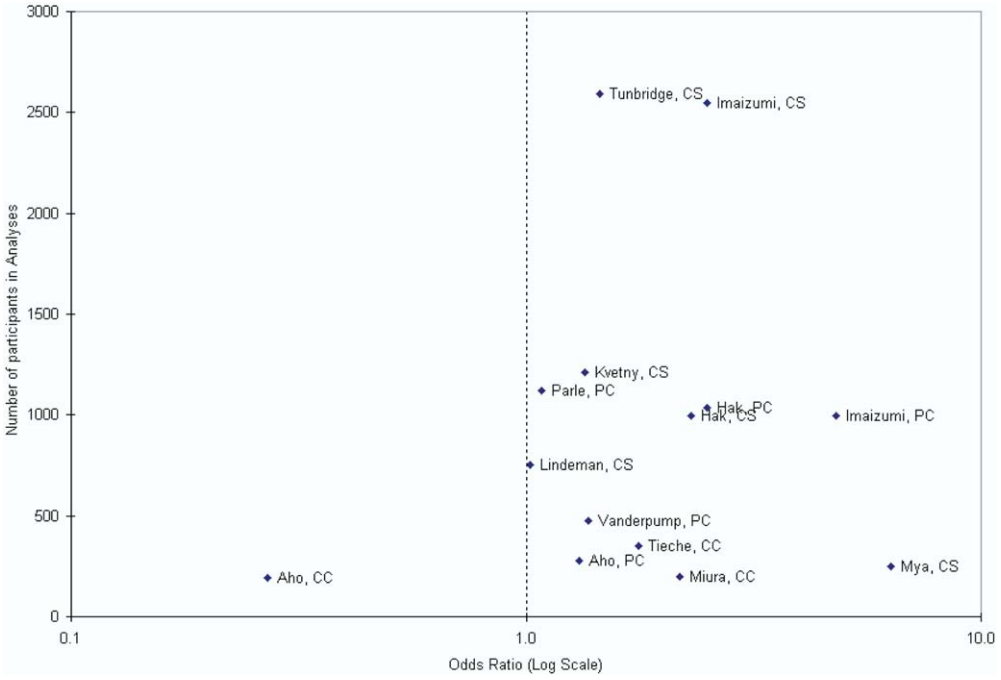

Figure 2 Funnel plot of included studies of the effect of subclinical hypothyroidism on the risk of CHD. ORs *(diamonds)* on a logarithmic scale are plotted against the sample size. The 1.0 line represents an OR of 1.0. CC = case-control study; CS = cross-sectional study; PC = prospective cohort study.

bias and quality problems in the original studies, publication bias, heterogeneity, and confounding.[24] To limit bias in the selection of included studies, we used broad inclusion criteria for studies that provided quantitative data on the risk of CHD in subjects with subclinical hypothyroidism, and then performed sensitivity analyses according to differences between the studies and methodologic study quality, as recommended.[24,61] Although the summary estimate showed a statistically significant higher risk of CHD associated with subclinical hypothyroidism, many of the original studies did not have statistically significant results. This might be because of the low power of the original studies to find an association, but the conclusion of meta-analyses of observational studies may also be limited by inherent biases and differences in study designs.[23] The sensitivity analyses performed did not suggest that our results meaningfully depended on differences in study designs or other study characteristics, but a meta-analysis cannot address bias and design flaws in the original studies. We cannot exclude the possibility that the observed association is a result of publication bias. Our graphical and statistical analyses showed that publication bias is unlikely, but the capacity to detect publication bias is limited when meta-analyses are based on a limited number of studies.[41,62]

We found weak evidence for statistical heterogeneity among individual study findings, and most of the heterogeneity resulted from a single relatively small cross-sectional study performed in nursing home residents.[16] The definitions of subclinical hypothyroidism and CHD were slightly different between the studies, but the sensitivity analyses pooling more homogeneous studies gave similar results. The different TSH cutoffs used reflect the absence of consensus to define subclinical hypothyroidism.[1,4,25-27] Some studies have a TSH cutoff less than 4.5 mU/L,[11,19,20,33] but the inclusion of subjects with an almost normal TSH value would be expected to blunt the effect of any observed associations, because some of these subjects may not have subclinical hypothyroidism. We were not able to exclude all subjects with inadequately treated overt hypothyroidism or nonthyroidal illness[63] because of the lack of these data in the original studies. However, limiting our analyses to studies that did exclude thyroid hormone users yielded similar results. Most individuals discovered to have subclinical hypothyroidism have a TSH less than 10 mU/L, and the risks of subclinical hypothyroidism are more uncertain in this group.[4] The increased risk of CHD we found might be driven by individuals with TSH of 10 mU/L or greater, but because these data have not been included in published studies we were not able to study the risk of CHD according to different TSH cutpoints. We could not assess the risk for specific CHD outcomes, such as myocardial infarction only, because of the lack of these subgroup analyses in the original studies. Part of the heterogeneity also might be accounted by differences in age and gender. One cross-sectional study performed subgroup analyses by age and found that the risk of CHD associated with subclinical hypothyroidism was higher and statistically significant only in subjects aged less than 50 years,[33] but no other study presented stratified analyses by age. No study presented stratified analyses by gender, but 1 prospective study in Japan found that men, but not women, with subclinical hypothyroidism had an increased total mortality for the first 6 years of follow-up (hazard ratio 1.9, 95% CI, 1.1-3.2).[15] Specific causes of death were not determined in women, and the significant increases in mortality in men with subclinical hypothyroidism were no longer apparent 10 years after baseline measurement.

In summary, our study suggests that subclinical hypothyroidism is associated with an increased risk of CHD. Potential alternative explanations for the observed results are bias in the original studies or publication bias. Despite these limitations, this study is based on the best currently available data and was performed according to commonly accepted recommendations to limit the problems associated with meta-analyses of observational studies.[24] If this result is confirmed in prospective studies with a large number of CHD events, clinical trials should assess whether thyroxine replacement reduces the risk of CHD in subjects with subclinical hypothyroidism.

ACKNOWLEDGMENTS

We thank Professor Jayne A. Franklyn (University of Birmingham, Birmingham, United Kingdom), Doctor Patrick Maissoneuve (European Institute of Oncology, Milano, Italy), Doctor Mark Vanderpump (Royal Free Hampsted NHS Trust, United Kingdom), Professor Mike Tunbridge (Oxford Radcliffe Hospitals, United Kingdom), and Doctor Jan Kvetny (Esjberg County Hospital, Denmark), who supplied at our request additional data from their studies in a written communication. We also thank Dan Moore, PhD (University of California, San Francisco), for helpful advice.

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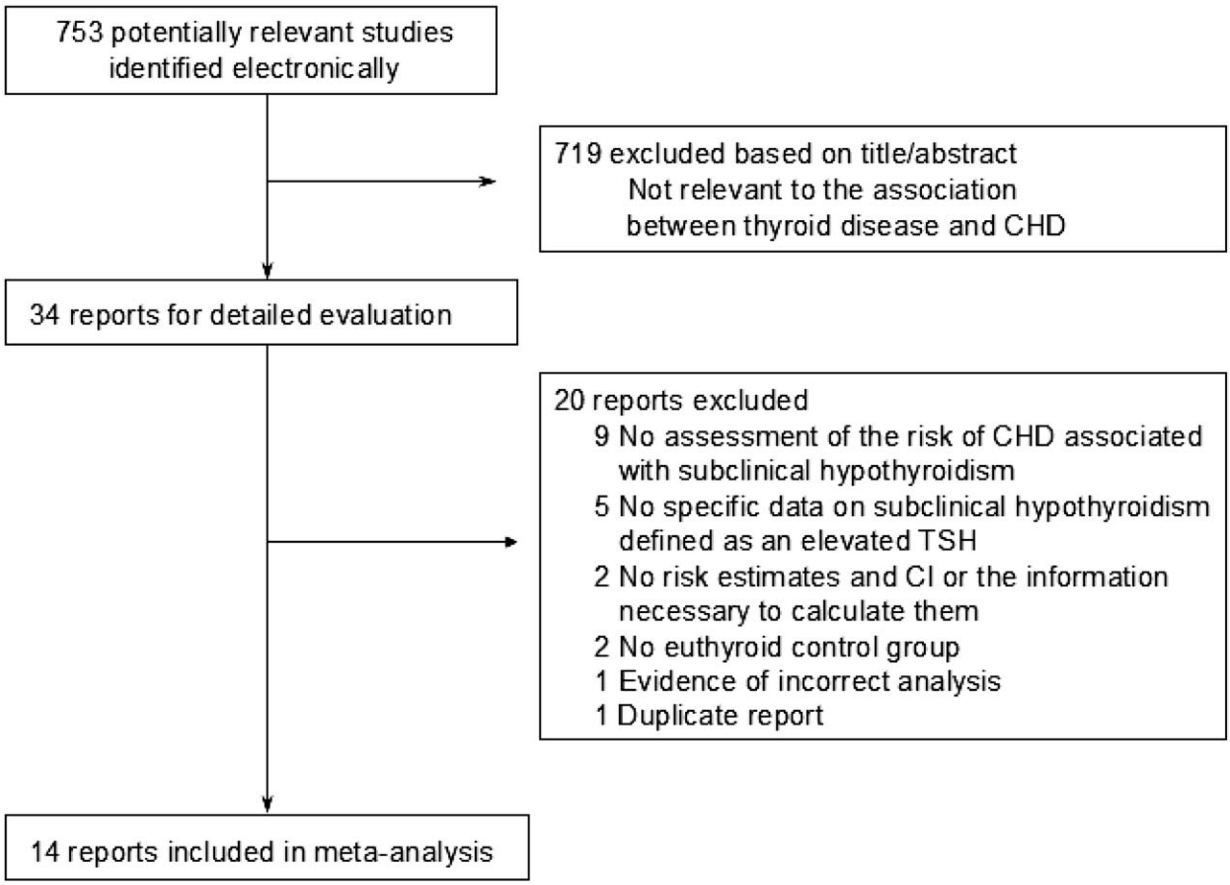
APPENDIX



Studies evaluated for inclusion in the meta-analysis. CHD = coronary heart disease; TSH = thyroid-stimulating hormone; CI = 95% confidence intervals.