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Subclinical Thyroid Dysfunction and the Risk for Fractures

A Systematic Review and Meta-analysis

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Background: Data on the association between subclinical thyroid dysfunction and fractures conflict.

Purpose: To assess the risk for hip and nonspine fractures associated with subclinical thyroid dysfunction among prospective cohorts.

Data Sources: Search of MEDLINE and EMBASE (1946 to 16 March 2014) and reference lists of retrieved articles without language restriction.

Study Selection: Two physicians screened and identified prospective cohorts that measured thyroid function and followed participants to assess fracture outcomes.

Data Extraction: One reviewer extracted data using a standardized protocol, and another verified data. Both reviewers independently assessed methodological quality of the studies.

Data Synthesis: The 7 population-based cohorts of heterogeneous quality included 50 245 participants with 1966 hip and 3281 nonspine fractures. In random-effects models that included the 5 higher-quality studies, the pooled adjusted hazard ratios (HRs) of participants with subclinical hyperthyroidism versus euthyrodism were 1.38 (95% CI, 0.92 to 2.07) for hip fractures and 1.20 (CI, 0.83 to 1.72) for nonspine fractures without statistical heterogeneity ($P = 0.82$ and 0.52, respectively; $I^2 = 0\%$). Pooled estimates for the 7 cohorts were 1.26 (CI, 0.96 to 1.65) for hip fractures and 1.16 (CI, 0.95 to 1.42) for nonspine fractures. When thyroxine recipients were excluded, the HRs for participants with subclinical hyperthyroidism were 2.16 (CI, 0.87 to 5.37) for hip fractures and 1.43 (CI, 0.73 to 2.78) for nonspine fractures. For participants with subclinical hypothyroidism, HRs from higher-quality studies were 1.12 (CI, 0.83 to 1.51) for hip fractures and 1.04 (CI, 0.76 to 1.42) for nonspine fractures (P for heterogeneity = 0.69 and 0.88, respectively; $I^2 = 0\%$).

Limitations: Selective reporting cannot be excluded. Adjustment for potential common confounders varied and was not adequately done across all studies.

Conclusion: Subclinical hyperthyroidism might be associated with an increased risk for hip and nonspine fractures, but additional large, high-quality studies are needed.

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About 10% of women and 3% of men older than 60 years have subclinical hypothyroidism (1–3), and prevalence increases with age. Subclinical hypothyroidism is defined as elevated thyroid-stimulating hormone (TSH) and normal free thyroxine (FT_4) levels (4). Subclinical hyperthyroidism, defined as decreased TSH and normal FT_4 and triiodothyronine (T_3) levels (4), is less common and affects about 1.5% of women and 1% of men older than 60 years. Subclinical thyroid dysfunction has previously been associated with an increased risk for coronary heart disease and heart failure events (5–7).

Thyroid hormones influence the homeostasis and remodeling of bone (8). Overt hyperthyroidism is a risk factor for fractures (9). A few observational studies have also found an increased risk for fracture in persons with overt hypothyroidism (10, 11).

The association between subclinical thyroid dysfunction and fractures remains unclear. A prospective cohort study of 3567 elderly participants found an increased risk for hip fractures in men with endogenous subclinical hyperthyroidism and a similar trend in women, whereas subclinical hypothyroidism was associated with an increased risk for hip fracture in men only (12). Conversely, a case–cohort study of 1526 ambulatory men older than 65 years found no significant relationship between subclinical hyperthyroidism and fractures, but low-normal TSH levels were significantly associated with an increased risk for hip fractures (13). Other prospective studies (14) did not adjust for common relevant potential confounders between subclinical thyroid dysfunction and fractures, such as age, sex, body mass index, smoking, and corticosteroid use (15–24). Two meta-analyses of postmenopausal women with exogenous subclinical hyperthyroidism due to thyroxine substitution showed a reduction in bone mineral density (BMD), which is a surrogate marker for osteoporosis (25, 26). To our knowledge, no meta-analysis has been done on the risk for fractures related with subclinical thyroid dysfunction. Therefore, we did a meta-analysis to determine whether subclinical thyroid dysfunction and TSH levels were associated with an increased risk for fractures in prospective cohort studies.

Methods

Data Sources and Searches

We followed a standardized protocol to do this meta-analysis. Similar to our previous study (27), we conducted a systematic literature search for articles in any language on the association between subclinical thyroid dysfunction (both subclinical hypothyroidism and hyperthyroidism) and fractures published between 1946 and 16 March 2014 in the MEDLINE and EMBASE databases. In Ovid MEDLINE, we used the following broadly defined Medical Subject Headings: thyroid diseases, hypothyroidism,

Table 1. **Description and Results of Included Studies for the Effect of Subclinical Thyroid Dysfunction on the Risk for Fractures**

Study, Year (Reference)	Population, *n*	Mean Age, *y*	TSH Cutoff Level*	
			Subclinical Hypothyroidism, *n*	Subclinical Hyperthyroidism, *n*
MrOS, 2013 (13)‡	Men, 1513§	74	>4.78 mIU/L, 126	<0.55 mIU/L, 37
Rotterdam, 2008 (44) and 2013 (45)‡	Both sexes, 1473 (women, 59.3%)	68.5	>4.3 mIU/L, 65	<0.40 mIU/L, 56
CHS, 2010 (12)	Both sexes, 3567 (women, 61.5%)	73	4.5–20.0 mIU/L, 543	<0.45 mIU/L, 171
HUNT2, 2013 (36)	Both sexes, 25205 (women, 65.9%)	58.2	>3.5 mIU/L, 1877	<0.5 mIU/L, 558
SOF, 2001 (35)‡	Women, 428 (hip fractures) and 352 (nonspine fractures)‡‡	72	>5.5 mIU/L, NR	0.1–0.5 mIU/L, 23 (hip fractures) and 20 (nonspine fractures) ≤0.1 mIU/L, 22 (hip fractures) and 12 (nonspine fractures)§§
TEARS, 2010 (14)‡	Both sexes, all receiving thyroxine, 17 684 (women, 85.9%)	60.5	4.0–20 mIU/L, 1975	0.04–0.4 mIU/L, 3731 ≤0.03 mIU/L, 1070§§
Sheffield, 2008 (46)‡	Women, 375	64.6	4.5–20 mIU/L, 31	<0.45 mIU/L, 11

CHS = Cardiovascular Health Study; FT_4 = free thyroxine; HR = hazard ratio; HUNT2 = Nord Trøndelag Health Study 2; MrOS = Osteoporotic Fractures in Men Study; NR = not reported; SOF = Study of Osteoporotic Fractures; TEARS = Thyroid Epidemiology Audit and Research Study; TSH = thyroid-stimulating hormone.
* For the definition of subclinical thyroid dysfunction.
† Most adjusted HRs available. Data from men and women combined (if available).
‡ Unpublished data, including HRs, provided by the authors.
§ Random sample of the overall cohort.
‖ Data with exclusion of thyroxine recipients available.
¶ Data available for men and women separately.
** Estimates reported were stratified by sex, so the authors used fixed effects to combine them before conducting the meta-analysis to avoid double counting a study in the random-effects models.
†† The FT_4 level was measured if the TSH level was <0.2 mIU/L or >4.0 mIU/L, but participants with biochemically overt thyroid dysfunction were not excluded.
‡‡ Nested sample of the overall cohort. The authors provided HRs with adjustment for additional confounders, which had not been measured in all women and therefore reduced *n*. Hip fractures were not included in nonspine fractures.
§§ Lower levels used only for sensitivity analyses.
‖‖ One hip fracture occurring after a nonspine fracture could not be tracked.
¶¶ Crude data to prevent overfitting (only 1 hip fracture).

hyperthyroidism, thyroid hormones, thyrotropin, subclinical hyperthyroidism, subclinical hypothyroidism, subclinical dysthyroidism, subclinical thyroid, and fractures or osteoporosis. These headings were combined with the filter designed by *British Medical Journal* knowledge information specialists to identify randomized, controlled trials; cohorts; and case–control studies without year limitation or exclusion of comments, editorials, meta-analyses, practice guidelines, reviews, letters, journal correspondences, books, conference papers, or animal studies (28). We used a similar procedure in EMBASE. We also searched the bibliographies of key articles in the field and those included in this review, and we contacted authors for unpublished studies.

Study Selection

Similar to our previous study (27), 2 authors independently screened the abstracts and titles of the search results and retained articles on prospective cohorts studying the association between thyroid dysfunction and osteoporotic fractures. The same reviewers independently assessed the remaining full-text articles for eligibility on the basis of predefined criteria. Any disagreement was resolved by discussion with a third author. Because some prospective studies that measured thyroid function and assessed multiple outcomes may not have reported fracture outcomes in the abstract, we also assessed the full text and tables for reported fracture data in these studies. We included only studies that fulfilled the following a priori–defined criteria: measurement of thyroid function, prospective follow-up of participants, assessment of fracture outcomes, comparison group with euthyroidism, and provision of hazard ratios (HRs) or sufficient data to calculate them. We excluded studies that examined only persons with a history of overt thyroid dysfunction or thyroid cancer.

We considered nonspine, hip, and any fractures, but we excluded spine fractures because vertebral fracture age is difficult to assess without serial radiographs and the accuracy of self-report is poor (29).

Agreement among reviewers was 97.9% for the first screening of titles and abstracts ($\kappa = 0.69$) and 100% for full-text screening ($\kappa = 1.0$).

Data Extraction and Quality Assessment

We used a standardized data abstraction form to extract information about participant characteristics, the criteria used to define subclinical thyroid dysfunction, and fractures. We evaluated study quality using slightly updated criteria (27, 30), adding inclusion of testing for the assumption of proportional hazards. One physician reviewer extracted data, and another checked data. We assessed key indicators for the quality of the cohort studies

Table 1—**Continued**

Was FT_4 Level Measured and Normal?	Were Recipients of Thyroid Hormone Excluded?	Follow-up, *y*	Fractures (Overall Number of Fractures/Subclinical Hypothyroid; Euthyroid; Subclinical Hyperthyroid Subgroup)	HR (95% CI)†	
				Subclinical Hypothyroidism	Subclinical Hyperthyroidism
Yes	No (7.4% treated)‖	5.3 (mean)	Hip fractures (48/6; 40; 2)	1.29 (0.49–3.37)	2.41 (0.54–10.66)
			Nonspine fractures (106/10; 92; 4)	0.89 (0.44–1.79)	1.58 (0.56–4.49)
Yes	Yes	9.4 (mean)	Hip fractures (53/4; 45; 4)	1.81 (0.64–5.09)	1.61 (0.58–4.51)¶
			Nonspine fractures (249/12; 224; 13)	0.97 (0.54–1.74)¶	1.36 (0.78–2.38)¶
Yes	No (9.2% treated)‖	13 (median)	Hip fractures (331/54; 256; 21)	1.23 (0.85–1.77)¶**	1.71 (0.92–3.19)¶**
No††	Yes	12.5 (median)	Hip fractures (1006/99; 876; 31)	1.05 (0.84–1.31)¶	1.22 (0.85–1.77)¶
			Hip and forearm fractures (2212/204; 1948; 60)	1.05 (0.90–1.22)¶	1.09 (0.84–1.42)¶
No	No (11% treated)	3.7 (mean)	Hip fractures (139/0; 114; 11 for a TSH level of 0.1–0.5 mIU/L and 14 for a TSH level ≤0.1 mIU/L)	NR	1.36 (0.50–3.72)
			Nonspine fractures (93/0; 80; 8 for TSH level of 0.1–0.5 mIU/L, 5 for TSH level ≤0.1 mIU/L)	NR	1.95 (0.85–4.50)
No	No (100% treated)	4.5 (median)	Hip fractures (384/NR)	1.70 (1.24–2.31)¶	1.08 (0.84–1.39)¶
			Nonspine fractures (540/NR)	1.81 (1.38–2.36)¶	1.11 (0.90–1.37)¶
Yes	No (1.7% treated)‖	10 (median)	Hip fractures (5/NR)‖‖	NR	10.29 (1.07–99.31)¶¶
			Nonspine fractures (81/NR)	2.04 (1.03–4.02)	1.89 (0.59–6.07)

(31, 32): the population studied (convenience sample vs. population-based, which was defined as a random sample of the general population) and methods of fracture ascertainment and adjudication (considered adequate if done by an expert panel blinded to thyroid status using a clear outcome definition); assessment of the proportional hazard assumption; completeness of follow-up; and adjustment for potential confounders. We defined age, sex, body mass index, smoking, and corticosteroid use (15–24) as common relevant potential confounders for the relationship between subclinical thyroid dysfunction and fractures based on a literature search considering their prevalence and strength of association with fractures and thyroid dysfunction. We required adjustment for most of these risk factors and lack of violation of the proportional hazard assumption for a study to be rated as higher quality. If an article did not clearly mention one of these criteria, we considered that it had not been done. Two reviewers independently rated all studies for quality, and disagreement was resolved with a third reviewer.

We contacted the authors of all cohorts to request more detailed data on the association between subclinical thyroid dysfunction and fractures. We used the most adjusted HRs and 95% CIs available.

Data Synthesis and Statistical Analysis

We used TSH cutoff levels as reported by each cohort. If not otherwise specified by a cohort, we used a common definition of subclinical thyroid disease based on expert reviews (4, 33) and the definition used in the Cardiovascular Health Study (12, 34), as done in previous articles (5–7). Subclinical hypothyroidism was defined as a TSH level greater than 4.5 to 20.0 mIU/L and an FT_4 level in the reference range. Subclinical hyperthyroidism was defined as a TSH level less than 0.45 mIU/L and an FT_4 level in the reference range. Euthyroidism was defined as a TSH cutoff level from 0.45 to 4.5 mIU/L. For FT_4, we used study-specific cutoff levels because these measurements show greater intermethod variation than TSH. Three studies (14, 35, 36) did not include FT_4 in their definition of subclinical thyroid dysfunction. Two of these studies (35, 36) were included in the main analysis of the higher-quality studies, but we did a sensitivity analysis excluding studies without FT_4 measurement or with abnormal FT_4 because some participants may have overt thyroid dysfunction. Two of these studies differentiated between low and suppressed TSH levels (14, 35). We used data from the group with low but not suppressed TSH levels because, according to unpublished data in our previous individual-participant data analysis (7), about one fourth of persons with a TSH level less than 0.1 mIU/L had overt hyperthyroidism, but only about 5% of those with a TSH level greater than 0.1 mIU/L had overt hyperthyroidism.

We qualitatively synthesized data and assessed which participants were included, the definition of thyroid dysfunction, and which types of fractures were studied. First, for the higher-quality studies, we calculated pooled estimates and 95% CIs of the risk for subclinical hyperthyroidism and hypothyroidism on hip and nonspine fractures using random-effects models based on the Knapp–Hartung approach (37) to account for the uncertainty associated with statistical heterogeneity (tau-square estimation) and the small number of studies included (38). Second, we assessed overall pooled estimates for all studies using the same approach. Because the Cardiovascular Health Study only reported estimates stratified by sex, we used fixed effects to combine these estimates before pooling them with other cohorts (12).

To assess heterogeneity among studies, we quantified the Q statistic with a conservative P value of 0.10 (39) and used the I^2 statistic, which describes the total variation across studies attributable to heterogeneity rather than chance ($I^2 > 50\%$, indicating at least moderate statistical

Table 2. **Quality Assessment of Included Studies***

Study, Year (Reference)	Design†	Country	Setting, *n*	Formal Adjudication Procedures for Fractures‡
MrOS, 2013 (13)	Random sample of a prospective cohort§	United States	Clinical center, 6	Yes
Rotterdam, 2008 (44) and 2013 (45)	Prospective cohort study	The Netherlands	District, 1	Yes
CHS, 2010 (12)	Prospective cohort study	United States	Community, 4	No‖
HUNT2, 2013 (36)	Prospective cohort study	Norway	Region, 1	Yes
SOF, 2001 (35)	Nested case–cohort study	United States	Clinical center, 4	Yes
TEARS, 2010 (14)	Prospective cohort study	Scotland	Region, 1	NR
Sheffield, 2008 (46)	Prospective cohort study	United Kingdom	Town, 1	NR

BMI = body mass index; CHS = Cardiovascular Health Study; HUNT2 = Nord Trøndelag Health Study 2; ICD-9 = International Classification of Diseases, Ninth Revision; ICD-10 = International Classification of Diseases, Tenth Revision; MrOS = Osteoporotic Fractures in Men Study; NCSP = Nomesco Classification of Surgical Procedures; NR = not reported; SIFF-95 = third version of the national classification of surgical procedures; SOF = Study of Osteoporotic Fractures; TEARS = Thyroid Epidemiology Audit and Research Study.
* If an article did not clearly mention one of the quality measures (e.g., formal adjudication procedures, adjudication without knowledge of thyroid status, lost to follow-up, or adjustments made), we considered that it had not been done.
† All studies listed were population-based, which was defined as a random sample of the general population.
‡ Defined as having clear criteria for the outcome that was reviewed by experts for each potential case.
§ The sample was chosen randomly at the baseline clinic visit from the 5994 participants included in the MrOS cohort.
‖ Communicated by the investigator.
¶ 214 participants died.
** 3 participants were missing fracture outcomes among those who did not die.
†† Tested using log−log survival plots.
‡‡ Identification of outcomes by review of hospital records. Missing outcome data cannot formally be excluded because fractures treated in other hospitals might be missing.
§§ Refers to 1 hip fracture occurring after a nonspine fracture that could not be tracked.
‖‖ Assessed by graphical methods (log−log graphs) and the Schoenfeld test.

heterogeneity) (40). To explore sources of heterogeneity, we did several predefined sensitivity analyses from all included studies using random-effects models. We also did analyses stratified by age and sex. Stratified analysis were accompanied by interaction tests based on Z scores, which are defined as the difference in effect estimates between strata divided by the SE of the difference.

We used an adjusted rank correlation test to assess for publication bias (41). However, graphical and statistical methods may not be reliable because of their limited power due to the small number of studies included in our meta-analysis (42). All analyses were done by using Stata, version 12.1 (StataCorp, College Station, Texas).

Role of the Funding Source

The funding source had no role in defining questions, abstracting data, synthesizing results, or preparing or deciding to submit the manuscript for publication.

RESULTS

Study Selection

Of the 1185 reports initially identified, 1132 were excluded on the basis of their title and abstract because they were unrelated to the association between subclinical thyroid dysfunction and fractures or were not prospective studies with measurement of thyroid hormones (**Appendix Figure 1**, available at www.annals.org). After full-text review of the 53 selected articles, we excluded 46 studies that did not meet the inclusion criteria (**Appendix Table**, available at www.annals.org). Seven studies met all eligibility criteria and were included in the analyses.

Study Characteristics

Table 1 shows the study characteristics of included studies in our meta-analysis and the HRs for the associations between subclinical thyroid dysfunction and hip and nonspine fractures. These 7 studies included 50 245 par-

Table 2—**Continued**

Methods for Fracture Ascertainment	Adjudication Without Knowledge of Thyroid Status	Lost to Follow-up, %	Missing Outcome Data, %	Proportional Hazard Assumption	Adjustments
Contact by mail; central adjudication by physician review of radiology reports or radiographs	Yes‖	1.4‖	2‖	Not violated	Age, clinic site, race, BMI, physical activity score, alcohol intake, smoking, and corticosteroid or thyroid hormone use
Records from general practitioners and the Dutch National Hospital Registration system; review of all coded events by a medical expert	Yes	0.2‖¶	0.2‖**	Not violated‖††	Age, BMI, and sex
Telephone interview or clinical visit; hospital records coded with ICD-9	NR	0‖	0‖	Not violated	Age, race, self-reported health status, frailty status, smoking, alcohol use, height, weight, calcium supplementation, and the use of antiosteoporosis and thyroid-altering medication during follow-up
Hospital records (patient administration system), diagnoses coded with ICD-9, ICD-10, SIFF-95, or NCSP, and x-ray descriptions; validation by physicians, health secretaries, and nurses	NR	NR	NR‡‡	Not violated	Age, sex, BMI, and smoking status
Contact by mail; confirmation by review of radiographs or written radiology reports	Yes	1	1	Not violated	Thyroid hormone or oral estrogen use, previous hyperthyroidism, age, self-rated health, smoking, and BMI‖
Hospital records; diagnoses coded with ICD-9 or ICD-10	NR	NR	NR‡‡	Not violated	Age, sex, history of hyperthyroidism, history of osteoporotic fracture, and diabetic status
Questionnaire, general practitioner's notes, and request forms; confirmation by radiologist's report or orthopedist's notes	NR	2	1§§	Not violated‖‖	Age

ticipants with 1966 hip and 3281 nonspine fractures. Four cohorts included men and women, 2 cohorts included only women, and 1 cohort included only men. Follow-up ranged from 3.7 to 13 years. One cohort included only participants treated with thyroid hormone, and 2 cohorts excluded all treated participants. Most cohorts assessed subclinical hyperthyroidism and hypothyroidism, and 1 cohort assessed only subclinical hyperthyroidism. All studies used a second- or third-generation TSH assay.

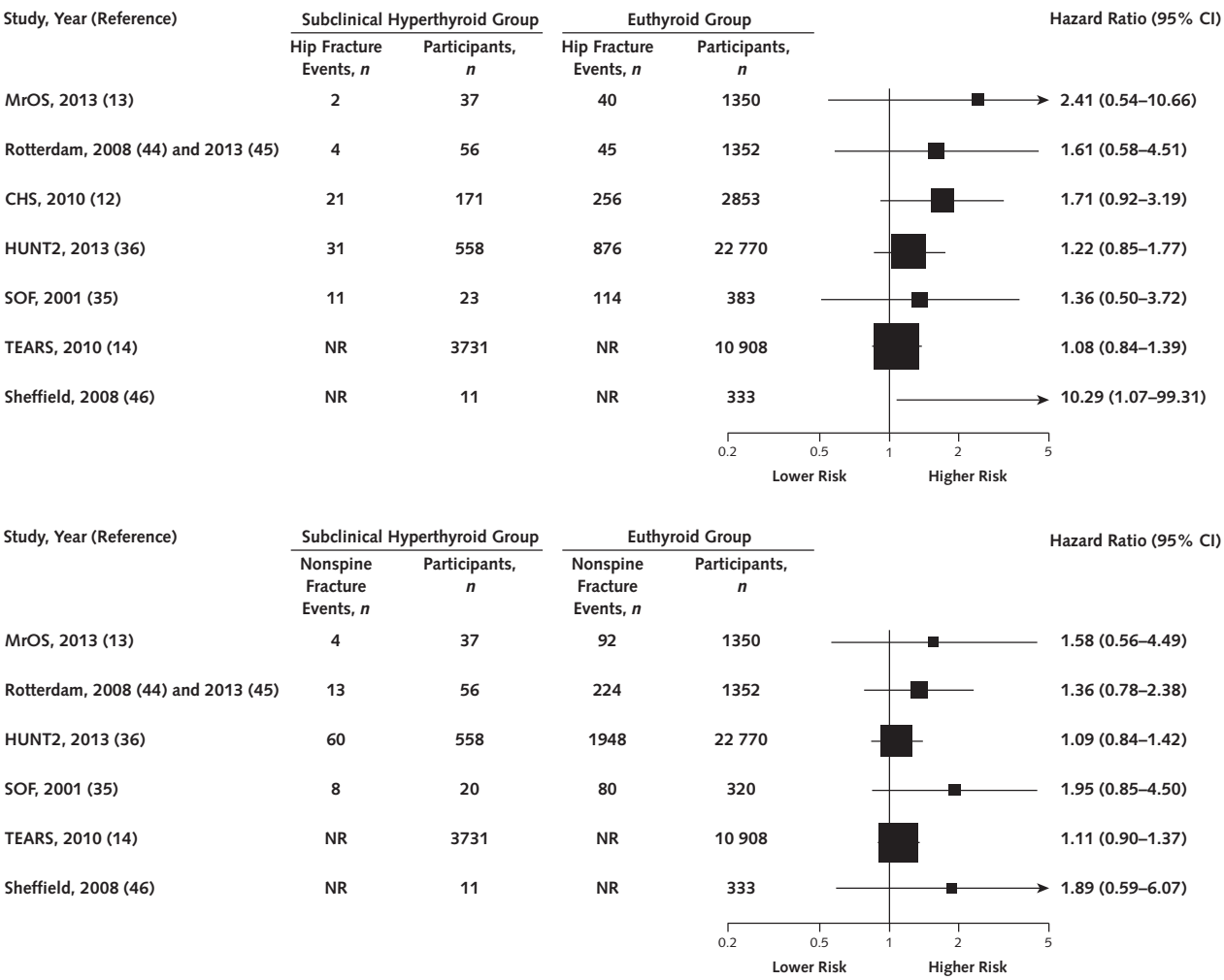
Description of Study Quality

The quality of included studies was heterogeneous. All studies were population-based (**Table 2**). Four used a formal adjudication procedure for fracture ascertainment, and 3 reported adjudication of fractures without knowledge of thyroid status. Five cohorts provided information on loss to follow-up, which was 2% or less. All cohorts reported nonviolation of the proportional hazard assumption. **Table 2** indicates the confounders that were adjusted for by the different studies by using appropriate multivariate analyses. Five of the studies reported HRs with adjustment for most of the aforementioned common relevant confounders, but 2 studies lacked such adjustment (14, 46). On the basis of the quality assessment in **Table 2**, with the request of the adjustment for most of these confounders and lack of violation of the proportional hazard assumption, 5 studies were rated higher quality and thus were included in the main pooled analysis (12, 13, 35, 36, 44).

Subclinical Hyperthyroidism and Hip Fractures

All studies found an increased risk for hip fractures associated with subclinical hyperthyroidism, and the Sheffield cohort had a statistically significant increased risk (**Figure**, *top*) (46). Among the higher-quality studies, 3 studies showed an HR greater than 1.5; the 2 largest studies found a lower HR, although TEARS (Thyroid Epidemiology Audit and Research Study) was not included in the analysis of the higher-quality studies because of inadequate adjustment for common relevant confounders and enrollment of only participants receiving long-term thyroxine medication. In a random-effects model with the 5 higher-quality studies, the pooled HR of subclinical hyperthyroidism and hip fractures was 1.38 (95% CI, 0.92 to 2.07) without evidence of heterogeneity (P for heterogeneity = 0.82; I^2 = 0%) (**Table 3**). Pooling estimates from all 7 included studies yielded similar results (**Table 3**). Including only studies that used a TSH cutoff level less than 0.45 mIU/L yielded an HR of 1.46 (CI, 0.62 to 3.45) for hip fractures. Pooled estimates for a TSH cutoff level of 0.1 mIU/L or less yielded an HR of 2.03 (CI, 0.27 to 15.00) with large CIs because only 2 studies reported such data. Results excluding all thyroid hormone recipients and thereby limiting the analysis to participants with endogenous subclinical hyperthyroidism indicated an increased risk for hip fracture (HR, 2.16 [CI, 0.87 to 5.37]). Predefined sensitivity analyses excluding studies that did not include FT_4 in their definition of subclinical thyroid dys-

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



CHS = Cardiovascular Health Study; HUNT2 = Nord Trøndelag Health Study 2; MrOS = Osteoporotic Fractures in Men Study; NR = not reported; SOF = Study of Osteoporotic Fractures; TEARS = Thyroid Epidemiology Audit and Research Study. **Top.** Risk for hip fractures. **Bottom.** Risk for nonspine fractures.

function, with the potential enrollment of participants with overt thyroid disease, yielded a slightly higher fracture risk. Stratified analyses by sex and age did not show statistical significance for interaction. A sensitivity analysis considering our predefined quality measures showed similar results for inclusion of studies using formal adjudication procedures. Results remained similar after excluding 1 study with a case–cohort design. After excluding a study that lacked FT_4 measurements, included only thyroxine-treated patients, and therefore compared overtreated participants with those in whom euthyroidism was achieved (14), the HR for hip fractures was 1.43 (CI, 0.99 to 2.06) and the duration of overtreatment was not reported.

Subclinical Hyperthyroidism and Nonspine Fractures

All included studies had a pattern of an increased risk for nonspine fractures associated with subclinical hyperthyroidism, although it was not statistically significant (**Figure**, *bottom*). The pooled HR, including estimates from the 4 higher-quality studies, was 1.20 (CI, 0.83 to 1.72), with weak evidence for statistical heterogeneity (P for heterogeneity = 0.52; I^2 = 0%). Pooling estimates from all studies and sensitivity analyses yielded similar results (**Table 3**) to those for the association between subclinical hyperthyroidism and hip fractures.

Subclinical Hypothyroidism and Fractures

Most individual studies showed a statistically nonsignificant pattern of an increased risk for hip fractures associated with subclinical hypothyroidism (**Appendix Figure 2**, available at www.annals.org). Pooled HRs from the higher-quality studies were 1.12 (CI, 0.83 to 1.51) for hip fractures and 1.04 (CI, 0.76 to 1.42) for nonspine fractures, both without evidence for heterogeneity across stud-

ies ($P = 0.69$ and 0.88, respectively; I^2 0%) (**Appendix Figure 2** and **Table 4**). Pooled estimates from studies with FT_4 measurements, which have excluded possibly enrolled participants with overt hypothyroidism, as well as from studies excluding thyroxine recipients, yielded similar results.

Evaluation of Potential Publication Bias

The rank correlation tests indicated little evidence of publication bias ($P > 0.05$) for all associations, although these tests are not sensitive due to the small number of studies (42).

Discussion

In this meta-analysis of 7 population-based, prospective cohort studies, pooled results from the 5 higher-quality studies indicated that subclinical hyperthyroidism might be associated with an increased risk for hip fractures (HR, 1.38 [CI, 0.92 to 2.07]) and nonspine fractures (HR, 1.20 [CI, 0.83 to 1.72]). When thyroxine recipients were excluded, the HRs for participants with subclinical hyperthyroidism were 2.16 (CI, 0.87 to 5.37) for hip fractures and 1.43 (CI, 0.73 to 2.78) for nonspine fractures. The relationship between subclinical hyperthyroidism and fractures seemed to be stronger among adults with a TSH cutoff level of 0.1 mIU/L or less, which indicated a possible dose–response relationship; however, CIs were large because only 2 studies provided such data. In subclinical hypothyroidism, the risk for fractures did not seem to be increased among the higher-quality studies.

To our knowledge, our study is the first systematic review and meta-analysis to examine the association between subclinical thyroid dysfunction and fracture risk. Our findings are supported by 2 previous meta-analyses of TSH-suppressive thyroxine therapy (25, 26), which found that in postmenopausal women, exogenous subclinical hyperthyroidism was significantly associated with a 0.91% annual decrease in bone mass (25). In addition, interventional studies on endogenous subclinical hyperthyroidism due to nodular goiter showed a 2% annual lower BMD than in postmenopausal women treated with an antithyroid drug or radioiodine (47, 48). In overt hyperthyroidism, a meta-analysis of 5 cohort or case–control studies showed that the risk for fractures normalized after 1 year of antithyroid therapy (9). A recent systematic review on the

Table 3. **Stratified and Sensitivity Analyses of the Association of Subclinical Hyperthyroidism and the Risk for Fractures**

Variable	Hip Fractures			Nonspine Fractures		
	Pooled HR (95% CI)	Studies, *n*	*P* for Heterogeneity*	Pooled HR (95% CI)	Studies, *n*	*P* for Heterogeneity*
Higher-quality studies						
Random effects	1.38 (0.92–2.07)	5	0.82	1.20 (0.83–1.72)	4	0.52
Fixed effects	1.38 (1.04–1.84)	5		1.20 (0.96–1.50)	4	
Estimates with all studies						
Random effects	1.26 (0.96–1.65)	7	0.36	1.16 (0.95–1.42)	6	0.67
Fixed effects	1.22 (1.01–1.47)	7		1.16 (1.00–1.35)	6	
Stratified and sensitivity analyses						
Definition of subclinical hyperthyroidism						
TSH cutoff level <0.45 mIU/L	1.46 (0.62–3.45)	4	0.128	1.15 (0.75–1.77)	3	0.56
TSH cutoff level ≤0.1 mIU/L	2.03 (0.27–15.00)	2†	0.51	1.97 (0.36–10.74)	2†	0.94
Exclusion of recipients of thyroxine	2.16 (0.87–5.37)	5	0.067	1.43 (0.73–2.78)	4	0.164
Measurement of FT_4 level and normal FT_4 level	1.90 (0.86–4.21)	4	0.49	1.47 (0.54–3.97)	3	0.87
Stratified by sex‡						
Women	1.22 (0.93–1.74)	6	0.44	1.19 (0.94–1.49)	5	0.63
Men	1.35 (0.60–3.03)	5	0.38	1.00 (0.44–2.26)	4	0.79
Stratified by mean age at enrollment in the cohorts§						
<65 y	1.21 (0.41–3.53)	3	0.140	1.11 (0.78–1.59)	3	0.66
≥65 y	1.67 (0.80–3.45)	4	0.94	1.53 (0.60–3.88)	3	0.78
Characteristics of study quality						
Formal fracture adjudication procedures and adjudication without knowledge of thyroid status	1.31 (0.78–2.19)	4	0.81	1.20 (0.83–1.72)	4	0.52
Studies excluded						
HUNT2 (36), included only hip and forearm fractures as nonspine fractures	1.40 (0.88–2.21)	6	0.26	1.20 (0.92–1.56)	5	0.58
TEARS (14), included only recipients of thyroxine	1.43 (0.99–2.06)	6	0.48	1.22 (0.89–1.66)	5	0.58
SOF (35), used case–cohort design	1.30 (0.90–1.86)	6	0.26	1.14 (0.92–1.42)	5	0.80

FT_4 = free thyroxine; HUNT2 = Nord Trøndelag Health Study 2; HR = hazard ratio; SOF = Study of Osteoporotic Fractures; TEARS = Thyroid Epidemiology Audit and Research Study; TSH = thyroid-stimulating hormone.
* $P > 0.10$; ratios are homogeneous.
† Did not measure FT_4 or triiodothyronine.
‡ P for interaction (sex) = 0.82 (hip fractures) and 0.69 (nonspine fractures).
§ P for interaction (age) = 0.63 (hip fractures) and 0.53 (nonspine fractures).

Table 4. **Stratified and Sensitivity Analyses of the Association of Subclinical Hypothyroidism and the Risk for Fractures**

Variable	Hip Fractures			Nonspine Fractures		
	Pooled HR (95% CI)	Studies, *n*	*P* for Heterogeneity*	Pooled HR (95% CI)	Studies, *n*	*P* for Heterogeneity*
Higher-quality studies						
Random effects	1.12 (0.83–1.51)	4	0.69	1.04 (0.76–1.42)	3	0.88
Fixed effects	1.12 (0.93–1.35)	4		1.04 (0.90–1.20)	3	
Estimates with all studies						
Random effects	1.30 (0.93–1.82)	5	0.157	1.28 (0.79–2.08)	5	0.004
Fixed effects	1.25 (1.06–1.46)	5		1.20 (1.06–1.36)	5	
Stratified and sensitivity analyses						
Definition of subclinical hypothyroidism						
Exclusion of recipients of thyroxine	1.10 (0.81–1.50)	4	0.60	1.11 (0.60–2.05)	4	0.151
Measurement of FT_4 level and normal FT_4 level	1.28 (0.63–2.62)	3	0.79	1.20 (0.39–3.64)	3	0.171
Stratified by sex†						
Women	1.29 (0.75–2.21)	4	0.078	1.38 (0.80–2.39)	4	0.015
Men	1.31 (0.44–3.94)	4	0.017	0.98 (0.43–2.24)	4	0.165
Stratified by mean age at enrollment in the cohorts‡						
<65 y	1.32 (0.06–28.04)	2	0.013	1.49 (0.54–4.10)	3	0.001
≥65 y	1.28 (0.63–2.62)	3	0.79	0.94 (0.05–17.24)	2	0.85
Characteristics of study quality						
Formal fracture adjudication procedures and adjudication without knowledge of thyroid status	1.08 (0.68–1.73)	3	0.57	1.04 (0.76–1.42)	3	0.88
Studies excluded						
HUNT2 (36), included only hip and forearm fractures as nonspine fractures	1.49 (1.03–2.14)	4	0.58	1.40 (0.73–2.68)	4	0.080
TEARS (14), included only recipients of thyroxine	1.12 (0.83–1.51)	4	0.69	1.10 (0.73–1.66)	4	0.27

FT_4 = free thyroxine; HUNT2 = Nord Trøndelag Health Study 2; HR = hazard ratio; TEARS = Thyroid Epidemiology Audit and Research Study.
* $P > 0.10$; ratios are homogeneous.
† P for interaction (sex) = 0.98 (hip fractures) and 0.50 (nonspine fractures).
‡ P for interaction (age) = 0.98 (hip fractures) and 0.77 (nonspine fractures).

clinical consequences of variations in thyroid hormones within the euthyroid reference range found good evidence for increased fracture risk associated with lower euthyroid TSH levels (49).

Different hypotheses have been made about the mechanisms of the association between subclinical hyperthyroidism and fractures. Subclinical hyperthyroidism has been associated with decreased BMD (25, 26) and may contribute to osteoporosis (50), which increases vulnerability to fractures (51). A study showed that thigh muscle strength decreases in subclinical hyperthyroidism and possibly leads to an increased risk for fall-related fractures (52, 53), although data on a direct association between subclinical hyperthyroidism and falls are lacking. The duration of subclinical hyperthyroidism may also play an important role in fracture development (47, 48, 51); however, this is difficult to assess, especially for endogenous subclinical hyperthyroidism (54). The observed lower risk for fractures when combining patients with exogenous and endogenous subclinical hyperthyroidism may be due to a presumably lower risk for fractures in patients with exogenous subclinical hyperthyroidism who may receive a reduced dosing of thyroid hormones, which limits the duration of the dysfunction. We found no evidence of a risk difference for fractures in women compared with men, despite the fact that women—especially postmenopausal women—have an increased risk for osteoporosis. In Americans aged 80 years, the 10-year probability of a hip fracture was 14% for women and 6% for men (55). Because all studies but 1 (35) did not have HRs adjusted for BMD, our analysis did not include BMD. When the Study of Osteoporotic Fractures (35) accounted for BMD, results did not substantially change the association between subclinical hyperthyroidism and fractures. However, the extent to which bone mass mediates the adverse effect of low TSH levels on fracture risk remains uncertain.

Prospective data on the association between subclinical hypothyroidism and fractures are scarce, and studies mainly investigate treated patients. A small randomized study showed a 1.3% reduction in lumbar BMD after 48 weeks of thyroxine treatment for subclinical hypothyroidism compared with placebo (56), and a large registry study in Denmark found an increased fracture risk for participants with overt hypothyroidism up to 4 years after initiation of thyroxine substitution (57). In our meta-analysis, we did not find an increased risk for fractures among participants with subclinical hypothyroidism. However, insufficient data prevented us from doing a sensitivity analysis to assess fracture risk among participants with subclinical hypothyroidism receiving thyroxine (compared with untreated participants). Overall, we did not find an effect of subclinical hypothyroidism on fractures, but the actual ef-

fect of thyroxine therapy on subclinical hypothyroidism cannot be assessed with the present study data.

Our meta-analysis of subclinical thyroid dysfunction and fractures has important strengths. First, by pooling the data of all available studies, we analyzed a total of 1966 hip and 3281 nonspine fractures in more than 50 000 participants, which increased power to detect an association (58). Second, only population-based prospective studies were included. Third, by contacting all principal investigators or coauthors of these 7 studies, we received additional data that allowed us to derive more uniform subgroup and sensitivity analyses.

Our study also has limitations. First, because it is a meta-analysis of observational studies, results have to be interpreted with caution, and potential biases, confounding, and heterogeneity must be carefully investigated (31, 59). The quality of the studies was heterogeneous. Some studies did not adequately adjust for all common potential confounders, which left a risk for residual confounding, and loss to follow-up and missing data were not reported in all studies. To address these limitations, we reported this study according to accepted guidelines for a meta-analysis of observational studies and did sensitivity analyses when appropriate (59). Furthermore, we excluded studies with major limitations from our main analysis and pooled only the 5 higher-quality studies. Second, selection bias may be present. To reduce this possibility, we used broad inclusion criteria and did sensitivity analyses stratified by design characteristics (59). Third, selective reporting cannot be excluded because tests and graphical assessment for publication bias are not sensitive enough owing to the small number of studies included in our meta-analysis (42). Fourth, our analysis included only European or U.S. cohorts, which limits the generalizability to other settings. Fifth, 6 of the 7 studies measured thyroid function at baseline only. Abnormal TSH levels can spontaneously normalize in 20% to 40% of persons after a mean follow-up of 2 to 4 years (60, 61), which may have decreased the potential associations. Sixth, only 4 of the 7 cohorts included the FT_4 level and no study included the T_3 level in its definition of subclinical thyroid disease. However, excluding studies (14, 35, 36) in a sensitivity analysis that did not include the FT_4 level yielded similar results with slightly higher point estimates. Finally, we conducted analyses stratified by age and sex using aggregate data at study level, but we might have missed a significant relationship because of ecological bias (62).

What are the clinical and research implications of these findings? Recent guidelines recommend treatment of subclinical hyperthyroidism in all persons older than 65 years (63), and our findings of a possibly increased fracture risk associated with subclinical hyperthyroidism are consistent with these guidelines, although there are no studies in which treatment resulted in a reduced fracture risk. Given the high prevalence of both osteoporosis and subclinical thyroid dysfunction in our aging populations, our findings may have public health implications. However, because this is a meta-analysis of observational studies, we cannot rule out that our findings are due to reasons other than subclinical thyroid dysfunction. A meta-analysis of individual-participant data that does not have potential aggregation bias could provide more insight through uniform TSH cutoff levels, standardized adjustment for potential confounding factors, and a thorough analysis of subgroups. To prove causality, large randomized, controlled trials are necessary to assess the efficacy of normalizing TSH levels in subclinical thyroid dysfunction associated with fracture risk (64). For subclinical hyperthyroidism, its low prevalence and the requirement for long follow-up make such trials a challenge. But for subclinical hypothyroidism, the ongoing TRUST (Thyroid Hormone Replacement for Subclinical Hypothyroidism) trial (ClinicalTrials.gov: NCT01660126) will clarify this issue (65).

In summary, our systematic review indicates that subclinical hyperthyroidism might be associated with an increased risk for hip and nonspine fractures, but additional large, high-quality studies are needed.

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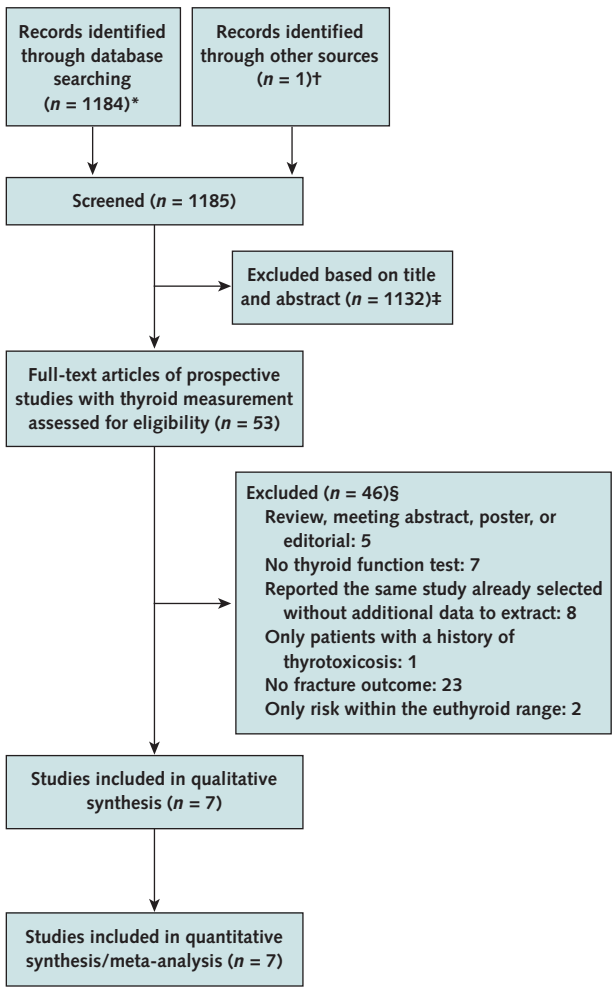
Appendix Figure 1. **Summary of evidence search and selection.**



Studies evaluated for inclusion in the meta-analysis (adapted from PRISMA Statement flow diagram [43]).
* Until 16 March 2014.
† From key articles in the field and contact with the authors (44).
‡ Exclusion criteria included records unrelated to the association between subclinical thyroid dysfunction and fractures or studies without prospective design and thyroid measurement.
§ For list of excluded full-text articles, see the **Appendix Table** (available at www.annals.org).

Appendix Table. Studies Excluded After Full-Text Screening

Reason for Exclusion	References
Review, meeting abstract, poster, or editorial	Aloumanis K, Eastell R, McCloskey EV. The effect of a history of thyroid disease in skeletal and muscle health and the risk of fractures in elderly women. Eur J Clin Invest. 2009;39:3. Compston JE. Thyroid hormone therapy and the skeleton. Clin Endocrinol (Oxf). 1993;39:519-20. Faber J, Galløe AM. Changes in bone mass during prolonged subclinical hyperthyroidism due to L-thyroxine treatment: a meta-analysis. Eur J Endocrinol. 1994;130:350-6. [PMID: 8162163] Lindstedt G, Nyström E. [Increased risk of bone-fragility-related fractures in TSH–suppressive thyroxine treatment]. Lakartidningen. 2002;99:2844-5. [PMID: 12143138] Herrick B. Subclinical hypothyroidism. Am Fam Physician. 2008;77:953-5.
No thyroid function test	Bach-Mortensen P, Hyldstrup L, Appleyard M, Hindsø K, Gebuhr P, Sonne-Holm S. Digital x-ray radiogrammetry identifies women at risk of osteoporotic fracture: results from a prospective study. Calcif Tissue Int. 2006;79:1-6. [PMID: 16868669] Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med. 1995;332:767-73. [PMID: 7862179] Huopio J, Honkanen R, Jurvelin J, Saarikoski S, Alhava E, Kröger H. Role of chronic health disorders in perimenopausal fractures. Osteoporos Int. 2005;16:1404-11. [PMID: 15739033] Ahmed LA, Schirmer H, Berntsen GK, Fønnebø V, Joakimsen RM. Self-reported diseases and the risk of non-vertebral fractures: the Tromsø study. Osteoporos Int. 2006;17:46-53. [PMID: 15838716] Turner MR, Camacho X, Fischer HD, Austin PC, Anderson GM, Rochon PA, et al. Levothyroxine dose and risk of fractures in older adults: nested case-control study. BMJ. 2011;342:d2238. [PMID: 21527461] Ko YJ, Kim JY, Lee J, Song HJ, Kim JY, Choi NK, et al. Levothyroxine dose and fracture risk according to the osteoporosis status in elderly women. J Prev Med Public Health. 2014;47:36-46. [PMID: 24570805] Nguyen TT, Heath H 3rd, Bryant SC, O'Fallon WM, Melton LJ 3rd. Fractures after thyroidectomy in men: a population-based cohort study. J Bone Miner Res. 1997;12:1092-9. [PMID: 9200009]
Reported the same study already selected without additional data to extract	Flynn RWV, Bonellie S, MacDonald TM, Leese GP. Increased risk of osteoporotic fracture in the thyroid population. Pharmacoepidemiology and Drug Safety. 2011;20:S29-S30. Hofman A, Breteler MM, van Duijn CM, Krestin GP, Pols HA, Stricker BH, et al. The Rotterdam Study: objectives and design update. Eur J Epidemiol. 2007;22:819-29. [PMID: 17955331] Lee JS, Buzkova P, Fink H, Vu J, Carbone L, Bauer D, et al. Subclinical thyroid dysfunction and incident hip fracture in older adults. Clinical and Translational Science. 2010;3:S11. Leese G, Flynn R. Is it safe for patients taking thyroxine to have a low but not suppressed serum TSH concentration? Endocrine Abstracts. 2010;21:OC5.6. Barrett-Connor E, Nielson CM, Orwoll E, Bauer DC, Cauley JA; Osteoporotic Fractures in Men Study Group. Epidemiology of rib fractures in older men: Osteoporotic Fractures in Men (MrOS) prospective cohort study. BMJ. 2010;340:c1069. [PMID: 20231246] Garin MC, Arnold AM, Lee JS, Robbins JA, Cappola AR. Subclinical thyroid dysfunction is not associated with hip fracture or lower bone mineral density in older adults. Endocrine Reviews. 2012;33. Bauer DC, Nevitt MC, Ettinger B, Stone K. Low thyrotropin levels are not associated with bone loss in older women: a prospective study. J Clin Endocrinol Metab. 1997;82:2931-6. [PMID: 9284722] Leese GP, Jung RT, Guthrie C, Waugh N, Browning MC. Morbidity in patients on L-thyroxine: a comparison of those with a normal TSH to those with a suppressed TSH. Clin Endocrinol (Oxf). 1992;37:500-3. [PMID: 1286519]
Only patients with a history of thyrotoxicosis	Hallengren B, Elmståhl B, Berglund J, Christensen SB, Elmståhl S, Johnell O, et al. No increase in fracture incidence in patients treated for thyrotoxicosis in Malmö during 1970-74. A 20-year population-based follow-up. J Intern Med. 1999;246:139-44. [PMID: 10447782]
No fracture outcome	Faber J, Jensen IW, Petersen L, Nygaard B, Hegedüs L, Siersbaek-Nielsen K. Normalization of serum thyrotrophin by means of radioiodine treatment in subclinical hyperthyroidism: effect on bone loss in postmenopausal women. Clin Endocrinol (Oxf). 1998;48:285-90. [PMID: 9578817] Appetecchia M. Effects on bone mineral density by treatment of benign nodular goiter with mildly suppressive doses of L-thyroxine in a cohort women study. Horm Res. 2005;64:293-8. [PMID: 16269872] Buscemi S, Verga S, Cottone S, Andronico G, D'Orio L, Mannino V, et al. Favorable clinical heart and bone effects of anti-thyroid drug therapy in endogenous subclinical hyperthyroidism. J Endocrinol Invest. 2007;30:230-5. [PMID: 17505157] Knudsen N, Faber J, Sierbaek-Nielsen A, Vadstrup S, Sørensen HA, Hegedüs L. Thyroid hormone treatment aiming at reduced, but not suppressed, serum thyroid-stimulating hormone levels in nontoxic goitre: effects on bone metabolism amongst premenopausal women. J Intern Med. 1998;243:149-54. [PMID: 9566644] Lin HC, Yang LY, Kang JH. Increased risk of pulmonary embolism among patients with hyperthyroidism: a 5-year follow-up study. J Thromb Haemost. 2010;8:2176-81. [PMID: 20738759] Ricken R, Bermpohl F, Schlattmann P, Bschor T, Adli M, Mönter N, et al. Long-term treatment with supraphysiological doses of thyroid hormone in affective disorders - effects on bone mineral density. J Affect Disord. 2012;136:e89-94. [PMID: 21757236] Acotto CG, Niepomniszcze H, Vega E, Mautalen CA. Ultrasound parameters and markers of bone turnover in hyperthyroidism: a longitudinal study. J Clin Densitom. 2004;7:201-8. [PMID: 15181264] Ceresini G, Morganti S, Rebecchi I, Bertone L, Ceda GP, Bacchi-Modena A, et al. A one-year follow-up on the effects of raloxifene on thyroid function in postmenopausal women. Menopause. 2004;11:176-9. [PMID: 15021447] Diamond T, Vine J, Smart R, Butler P. Thyrotoxic bone disease in women: a potentially reversible disorder. Ann Intern Med. 1994;120:8-11. [PMID: 8250460] Fujiyama K, Kiriyama T, Ito M, Kimura H, Ashizawa K, Tsuruta M, et al. Suppressive doses of thyroxine do not accelerate age-related bone loss in late postmenopausal women. Thyroid. 1995;5:13-7. [PMID: 7787427] Grimnes G, Emaus N, Joakimsen RM, Figenschau Y, Jorde R. The relationship between serum TSH and bone mineral density in men and postmenopausal women: the Tromsø study. Thyroid. 2008;18:1147-55. [PMID: 18925834] Gyulai L, Jaggi J, Bauer MS, Younkin S, Rubin L, Attie M, et al. Bone mineral density and L-thyroxine treatment in rapidly cycling bipolar disorder. Biol Psychiatry. 1997;41:503-6. [PMID: 9034547] Límanová Z, Stepán J. [Increased risk of osteoporosis in thyroid hormone substitution therapy]. Cas Lek Cesk. 1990;129:625-7. [PMID: 2354492] Linde J, Friis T. Osteoporosis in hyperthyroidism estimated by photon absorptiometry. Acta Endocrinol (Copenh). 1979;91:437-48. [PMID: 474036]

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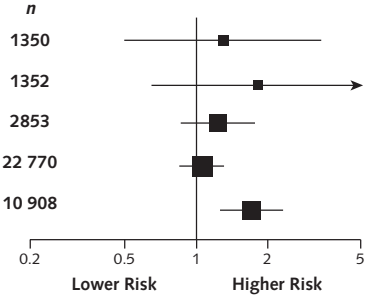
Appendix Table—Continued

Reason for Exclusion	References
	Marcocci C, Golia F, Bruno-Bossio G, Vignali E, Pinchera A. Carefully monitored levothyroxine suppressive therapy is not associated with bone loss in premenopausal women. J Clin Endocrinol Metab. 1994;78:818-23. [PMID: 8157704] Obermayer-Pietsch B, Dobnig H, Warnkross H, Dimai HP, Weber K, Berghold A, et al. Variable bone mass recovery in hyperthyroid bone disease after radioiodine therapy in postmenopausal patients. Maturitas. 2000;35:159-66. [PMID: 10924842] Stall GM, Harris S, Sokoll LJ, Dawson-Hughes B. Accelerated bone loss in hypothyroid patients overtreated with L-thyroxine. Ann Intern Med. 1990;113:265-9. [PMID: 2375563] Stamato FJ, Amarante EC, Furlanetto RP. Effect of combined treatment with calcitonin on bone densitometry of patients with treated hypothyroidism. Rev Assoc Med Bras. 2000;46:177-81. [PMID: 11022359] Chirico V, Rigoli L, Piraino B, La Rosa M, Salpietro C, Arrigo T. Endocrinopathies in beta-thalassemia major: Evidences from ten years of follow-up and evaluation of combined iron chelation therapy. Hormone Research in Paediatrics. 2013;80:318. Legroux-Gérot I, Vignau J, d'Herbomez M, Flipo RM, Cortet B. Predictive factors of change in BMD at 1 and 2 years in women with anorexia nervosa: a study of 146 cases. Osteoporos Int. 2012;23:2855-61. [PMID: 22349911] Baldini M, Vigna L, Gallazzi M, Orsatti A, Legnani L, Peracchi G, et al. Age and postmenopausal state related risk of axial bone demineralization in goitrous women treated with L-thyroxine. A longitudinal study. Rivista Italiana di Biologia e Medicina. 1996;16:85-90. La Vignera S, Vicari E, Tumino S, Ciotta L, Condorelli R, Vicari LO, et al. L-thyroxin treatment and post-menopausal osteoporosis: relevance of the risk profile present in clinical history. Minerva Ginecol. 2008;60:475-84. [PMID: 18981975] Fowler PB, McIvor J, Sykes L, Macrae KD. The effect of long-term thyroxine on bone mineral density and serum cholesterol. J R Coll Physicians Lond. 1996;30:527-32.
Only risk within the euthyroid range	Hoeg A, Gogakos A, Murphy E, Mueller S, Köhrle J, Reid DM, et al. Bone turnover and bone mineral density are independently related to selenium status in healthy euthyroid postmenopausal women. J Clin Endocrinol Metab. 2012;97:4061-70. [PMID: 22904175] Murphy E, Glüer CC, Reid DM, Felsenberg D, Roux C, Eastell R, et al. Thyroid function within the upper normal range is associated with reduced bone mineral density and an increased risk of nonvertebral fractures in healthy euthyroid postmenopausal women. J Clin Endocrinol Metab. 2010;95:3173-81. [PMID: 20410228]

Appendix Figure 2. Forest plots for subclinical hypothyroidism.

Study, Year (Reference)	Subclinical Hypothyroid Group		Euthyroid Group		Hazard Ratio (95% CI)
	Hip Fracture Events, *n*	Participants, *n*	Hip Fracture Events, *n*	Participants, *n*	
MrOS, 2013 (13)	6	126	40	1350	1.29 (0.49–3.37)
Rotterdam, 2008 (44) and 2013 (45)	4	65	45	1352	1.81 (0.64–5.09)
CHS, 2010 (12)	54	543	256	2853	1.23 (0.85–1.77)
HUNT2, 2013 (36)	99	1877	876	22 770	1.05 (0.84–1.31)
TEARS, 2010 (14)	NR	1975	NR	10 908	1.70 (1.24–2.31)



Study, Year (Reference)	Subclinical Hypothyroid Group		Euthyroid Group		Hazard Ratio (95% CI)
	Nonspine Fracture Events, *n*	Participants, *n*	Nonspine Fracture Events, *n*	Participants, *n*	
MrOS, 2013 (13)	10	126	92	1350	0.89 (0.44–1.79)
Rotterdam, 2008 (44) and 2013 (45)	12	65	224	1352	0.97 (0.54–1.74)
HUNT2, 2013 (36)	204	1877	1948	22 770	1.05 (0.90–1.22)
TEARS, 2010 (14)	NR	1975	NR	10 908	1.81 (1.38–2.36)
Sheffield, 2008 (46)	NR	31	NR	333	2.04 (1.03–4.02)

CHS = Cardiovascular Health Study; HUNT2 = Nord Trøndelag Health Study 2; MrOS = Osteoporotic Fractures in Men Study; NR = not reported; TEARS = Thyroid Epidemiology Audit and Research Study. **Top.** Risk for hip fractures. **Bottom.** Risk for nonspine fractures.