Article:
Blum, M.R., Bauer, D.C., Collet, T-H. et al. (31 more authors) (2015) Subclinical Thyroid Dysfunction and Fracture Risk: A Meta-analysis. The Journal of the American Medical Association (JAMA), 313 (20). pp. 2055-2065. ISSN 0098-7484

https://doi.org/10.1001/jama.2015.5161

HHS Public Access

Author manuscript

JAMA. Author manuscript; available in PMC 2016 January 27.

Published in final edited form as:

JAMA. 2015 May 26; 313(20): 2055–2065. doi:10.1001/jama.2015.5161.

Subclinical Thyroid Dysfunction and Fracture Risk:

A Meta-analysis

Manuel R. Blum, MD, **Douglas C. Bauer, MD**, **Tinh-Hai Collet, MD**, **Howard A. Fink, MD, MPH**, **Anne R. Cappola, MD, ScM**, **Bruno R. da Costa, PhD**, **Christina D. Wirth, MD**, **Robin P. Peeters, MD, PhD**, **Bjørn O. Åsvold, MD, PhD**, **Wendy P. J. den Elzen, PhD**, **Robert N. Luben, PhD**, **Misa Imaizumi, MD, PhD**, **Alexandra P. Bremner, PhD**, **Apostolos Gogakos, MD, PhD**, **Richard Eastell, MD**, **Patricia M. Kearney, MD, PhD, MPH**, **Elsa S. Strotmeyer, MD, PhD**, **Erin R. Wallace, PhD**, **Mari Hoff, MD, PhD**, **Graziano Ceresini, MD, PhD**, **Fernando Rivadeneira, MD, PhD**, **André G. Uitterlinden, PhD**, **David J. Stott, MD, PhD**, **Rudi G. J. Westendorp, MD, PhD**, **Kay-Tee Khaw, MD**, **Arnuf Langhammer, MD, PhD**, **Luigi Ferrucci, MD, PhD**, **Jacobijn Gussekloo, MD, PhD**, **Graham R. Williams, MBBS, PhD**, **John P. Walsh, MBBS, PhD**, **Peter Jüni, MD**, **Drahomir Aujesky, MD, MSc**, and **Nicolas Rodondi, MD, MAS for the Thyroid Studies Collaboration**

Department of General Internal Medicine, Inselspital, Bern University Hospital, Bern, Switzerland (Blum, Wirth, Aujesky, Rodondi); Departments of Medicine and Epidemiology and Biostatistics, University of California, San Francisco (Bauer); Service of Endocrinology, Diabetes and Metabolism, University Hospital of Lausanne, Lausanne, Switzerland (Collet); Department of Medicine, University of Minnesota School of Medicine, Minneapolis (Fink); Geriatric Research Education and Clinical Center, VA Medical Center, Minneapolis, Minnesota (Fink); University of Pennsylvania School of Medicine, Philadelphia (Cappola); Associate Editor, *JAMA* (Cappola); Department of Physical Therapy, Nicole Wertheim College of Nursing and Health Science, Florida International University, Miami (da Costa); Department of Internal Medicine, Erasmus Medical Center, Rotterdam, the Netherlands (Peeters, Rivadeneira, Uitterlinden); Department of Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands (Peeters, Rivadeneira, Uitterlinden); Department of Public Health and General Practice, Norwegian University of Science and Technology, Trondheim, Norway (Åsvold, Hoff, Langhammer); Department of Endocrinology, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway (Åsvold); Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, the Netherlands (den Elzen, Gussekloo); Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom (Luben, Khaw); Radiation Effects Research Foundation, Nagasaki, Japan (Imaizumi); School of Population Health, University of Western Australia, Crawley, WA, Australia (Bremner); Department of Medicine, Imperial College London, London, United Kingdom (Gogakos, Williams); Department of Human Metabolism, University of Sheffield, Sheffield, United Kingdom (Eastell); Department of Epidemiology and Public Health, University College Cork, Cork, Ireland (Kearney); Department of Epidemiology, University of Pittsburgh, Pittsburgh,

Corresponding Author: Nicolas Rodondi, MD, MAS, Department of General Internal Medicine, Inselspital, University of Bern, 3010 Bern, Switzerland (nicolas.rodondi@insel.ch).

Disclaimer: Dr Cappola, a *JAMA* Associate Editor, was not involved in the review of or decision to publish this work.

Additional Contributions: The contribution of inhabitants, general practitioners, and pharmacists of the Ommoord district to the Rotterdam Study is gratefully acknowledged.

Pennsylvania (Strotmeyer); Cardiovascular Health Research Unit, University of Washington, Seattle (Wallace); Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway (Hoff); Department of Clinical and Experimental Medicine, Geriatric Endocrine Unit, University Hospital of Parma, Parma, Italy (Ceresini); Institute of Cardiovascular and Medical Sciences, University of Glasgow, United Kingdom (Stott); Department of Public Health, University of Copenhagen, Copenhagen, Denmark (Westendorp); National Institute on Aging, National Institutes of Health, Baltimore, Maryland (Ferrucci); School of Medicine and Pharmacology, University of Western Australia, Crawley, WA, Australia (Walsh); Department of Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Nedlands, WA, Australia (Walsh); Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland (Jüni)

Abstract

IMPORTANCE—Associations between subclinical thyroid dysfunction and fractures are unclear and clinical trials are lacking.

OBJECTIVE—To assess the association of subclinical thyroid dysfunction with hip, nonspine, spine, or any fractures.

DATA SOURCES AND STUDY SELECTION—The databases of MEDLINE and EMBASE (inception to March 26, 2015) were searched without language restrictions for prospective cohort studies with thyroid function data and subsequent fractures.

DATA EXTRACTION—Individual participant data were obtained from 13 prospective cohorts in the United States, Europe, Australia, and Japan. Levels of thyroid function were defined as euthyroidism (thyroid-stimulating hormone [TSH], 0.45–4.49 mIU/L), subclinical hyperthyroidism (TSH <0.45 mIU/L), and subclinical hypothyroidism (TSH ≥4.50–19.99 mIU/L) with normal thyroxine concentrations.

MAIN OUTCOME AND MEASURES—The primary outcome was hip fracture. Any fractures, nonspine fractures, and clinical spine fractures were secondary outcomes.

RESULTS—Among 70 298 participants, 4092 (5.8%) had subclinical hypothyroidism and 2219 (3.2%) had subclinical hyperthyroidism. During 762 401 person-years of follow-up, hip fracture occurred in 2975 participants (4.6%; 12 studies), any fracture in 2528 participants (9.0%; 8 studies), nonspine fracture in 2018 participants (8.4%; 8 studies), and spine fracture in 296 participants (1.3%; 6 studies). In age- and sex-adjusted analyses, the hazard ratio (HR) for subclinical hyperthyroidism vs euthyroidism was 1.36 for hip fracture (95% CI, 1.13–1.64; 146 events in 2082 participants vs 2534 in 56 471); for any fracture, HR was 1.28 (95% CI, 1.06–1.53; 121 events in 888 participants vs 2203 in 25 901); for nonspine fracture, HR was 1.16 (95% CI, 0.95–1.41; 107 events in 946 participants vs 1745 in 21 722); and for spine fracture, HR was 1.51 (95% CI, 0.93–2.45; 17 events in 732 participants vs 255 in 20 328). Lower TSH was associated with higher fracture rates: for TSH of less than 0.10 mIU/L, HR was 1.61 for hip fracture (95% CI, 1.21–2.15; 47 events in 510 participants); for any fracture, HR was 1.98 (95% CI, 1.41–2.78; 44 events in 212 participants); for nonspine fracture, HR was 1.61 (95% CI, 0.96–2.71; 32 events in 185 participants); and for spine fracture, HR was 3.57 (95% CI, 1.88–6.78; 8 events in 162 participants). Risks were similar after adjustment for other fracture risk factors. Endogenous subclinical hyperthyroidism (excluding thyroid medication users) was associated with HRs of 1.52

(95% CI, 1.19–1.93) for hip fracture, 1.42 (95% CI, 1.16–1.74) for any fracture, and 1.74 (95% CI, 1.01–2.99) for spine fracture. No association was found between subclinical hypothyroidism and fracture risk.

CONCLUSIONS AND RELEVANCE—Subclinical hyperthyroidism was associated with an increased risk of hip and other fractures, particularly among those with TSH levels of less than 0.10 mIU/L and those with endogenous subclinical hyperthyroidism. Further study is needed to determine whether treating subclinical hyperthyroidism can prevent fractures.

Overt hyperthyroidism is an established risk factor for osteoporosis and fractures.[1] More subtle alterations in thyroid function found in subclinical thyroid dysfunction, defined as abnormal thyroid-stimulating hormone (TSH) with normal free thyroxine (FT_4), could also be associated with increased fracture risk and bone loss.[2–4]

In prospective cohort studies, data about the association between subclinical thyroid dysfunction and fracture risk are in conflict because of inclusion of participants with overt thyroid disease[3,5] and small sample sizes of participants with thyroid dysfunction[6,7] or fracture events.[8] To our knowledge, no clinical trial has examined the effect of treating subclinical thyroid dysfunction on fracture risks. A recent study-level meta-analysis of prospective cohorts found an increased fracture risk in subclinical hyperthyroidism, but interpretation was limited by population heterogeneity, discrepant definitions of fractures, and differing TSH cutoffs for defining subclinical thyroid dysfunction,[9] which could not be addressed in a study-level meta-analysis.

For these reasons, we performed a pooled analysis of individual participant data of multiple large cohorts that assessed the association of subclinical thyroid dysfunction with risk for hip fractures, as well as nonspine, clinical spine, and fractures of any location. This approach allowed exploration of the relationship of age, sex, and TSH levels with the association of subclinical thyroid dysfunction and fractures, and is considered an optimal approach for combining evidence.[10]

Methods

This individual participant data analysis was performed according to a predefined protocol.[11]

Study Selection

We performed a systematic literature search in MEDLINE and EMBASE, from inception to March 26, 2015, without language restriction, for prospective cohorts of adults with baseline TSH and FT_4 levels12 and follow-up for incident fractures. We excluded studies that included only participants with overt thyroid dysfunction or individuals taking thyroid-altering medications (thyroxine, iodine, oral corticosteroids, amiodarone, antithyroid drugs). We conducted the search on an Ovid (MEDLINE) server using broadly defined Medical Subject Headings: *thyroid diseases*, *hypothyroidism*, *hyperthyroidism*, *thyroid hormones*, *thyrotropin*, *subclinical hyperthyroidism*, *subclinical hypothyroidism*, *subclinical dysthyroidism or subclinical thyroid*, and *fractures or osteoporosis*. We used a filter to extract prospective studies (MEDLINE cohort-study filter)[13] but without year limitation.

The search was also conducted in EMBASE using similar terms. We searched bibliographies of key articles in the field. Two authors (M.R.B. and C.D.W.) independently screened the abstracts of the search results and independently assessed the remaining full-text articles for eligibility. Any disagreement was resolved with the help of a third author (D.C.B.).[9] We also asked cohorts of the Thyroid Studies Collaboration[12,14–16] for unpublished prospective fracture data.

All qualifying cohorts were invited to join and provide individual participant data about baseline thyroid function, participant characteristics, bone metabolism–altering and thyroid medications, and fracture data. We conducted this individual participant data analysis in collaboration with investigators from each cohort to resolve data issues.[17] Individual cohort results were validated against published results. Four cohorts that had not previously published fracture data[18–21] provided exact procedures for data collection and adjudication of fracture data. For comparability with other cohorts in the present analysis, we used the random sample of the Osteoporotic Fractures in Men (MrOS) Study[7] from 5994 participants at the baseline visit.[9]

Definition of Subclinical Thyroid Dysfunction

We used a uniform TSH threshold to maximize comparability, based on previously established thresholds.[12] Euthyroidism was defined as having a TSH level of 0.45 to 4.49 mIU/L. Subclinical hyperthyroidism was defined as having a TSH level of less than 0.45 mIU/L with normal FT_4 levels and was further stratified as suppressed TSH (<0.10 mIU/L) and low but not suppressed TSH (0.10–0.44 mIU/L). Subclinical hypothyroidism was defined as having a TSH level of 4.50 to 19.99 mIU/L with normal FT_4 levels. Participants with a missing FT_4 level and a TSH level within the range for subclinical thyroid dysfunction (1024 participants) were considered as having subclinical thyroid dysfunction because most adults with TSH levels in this range have subclinical and not overt thyroid dysfunction (eTable 1 in Supplement 1).[22] Cohorts using first-generation TSH assays were excluded from analyses of subclinical hyperthyroidism because of insufficient sensitivity of first-generation thyroid assays.[23] Because of greater interstudy method variation, we used cohort-specific cutoffs for FT_4 and triiodothyronine (T_3) levels (eTable 1 in Supplement 1). We performed a sensitivity analysis on persistent thyroid dysfunction using repeated TSH and FT_4 measurements (available in 5 cohorts; follow-up duration in eTable 5 in Supplement 1). We performed additional sensitivity analyses excluding participants using thyroid-altering medications to estimate the risk associated with endogenous subclinical thyroid dysfunction, and excluding participants with missing FT_4 levels or abnormal total or free T_3 levels (measured in 4 out of 13 cohorts).

Outcomes

Our a priori–defined primary outcome was incident hip fracture. Secondary outcomes were incident fractures of any location, nonspine, and clinical spine fractures. We standardized outcome definitions (eTable 1 in Supplement 1). Incident hip fractures typically included fractures of the femoral neck, pertrochanteric, and subtrochanteric fractures, excluding pathologic and periprosthetic fractures. Incident nonspine fractures were defined as hip or any other nonpathologic fracture excluding the spine, and excluding fractures of the skull or

face, ankle, finger, and toe, which are not typically affected by increased bone fragility. Incident spine fractures were defined as clinically diagnosed and radiographically confirmed thoracic and lumbar spine fractures, excluding cervical and sacral fractures because these usually occur due to trauma that is unrelated to bone fragility. We restricted our spine fracture outcome to those that were clinically diagnosed and did not consider spine fractures identified only by scheduled radiographs, to focus analyses on associations with outcomes that are more likely to be symptomatic[24] and therefore of greater clinical relevance to patients.[25] The outcome of any fracture was defined as the first event of either nonspine or clinically diagnosed spine fracture. Cohorts with fracture data only for parts of the skeleton, such as 1 study with hip fracture data only,[8] were not included for this outcome.

In a secondary analysis, we compared fracture risk between thyroxine-treated and untreated participants at baseline, irrespective of thyroid function test results, to assess fracture risk associated with thyroxine use.

To evaluate study quality, we used the individual criteria of the Newcastle-Ottawa Quality Assessment Scale[26] (eTable 2 and eMethods in Supplement 1). We performed sensitivity analyses excluding cohorts that did not meet different individual criteria of this scale.

Statistical Analyses

We used established methods[10,17] with a 2-step approach, first analyzing the association of subclinical thyroid dysfunction with outcomes using separate Cox proportional hazard models for each cohort (Stata version 12.1), and in a second step calculating pooled estimates using random-effects models.[27] Time to event was calculated for each outcome from baseline to first event. For cohorts with no event in some subgroups of thyroid function, penalized maximum likelihood estimation models[28] were used to derive hazard ratios (HRs) and 95% CIs (SAS version 9.3). Strata with fewer than 6 participants per cohort were excluded from pooling due to unreliable estimates. We summarized results using forest plots (Review Manager version 5.3.3). We calculated the variance estimate τ^2 as a measure of heterogeneity in estimates across cohorts. τ^2values were prespecified to indicate low (≤0.04), moderate (>0.04–<0.36), and high (≥0.36) to indicate heterogeneity.[29] *P* values of less than .05 were considered as significant and testing was 2-sided.

Primary analyses were adjusted for age and sex, and then for other known risk factors for fractures because some might be potential mediators (eg, body mass index [BMI]) of the association between subclinical thyroid dysfunction and fractures. Based on a literature search of potential confounders for this association, taking into account their prevalence and strength of their association with fractures and possible influence on thyroid function, we further adjusted for BMI (calculated as weight in kilograms divided by height in meters squared)[30] and smoking status,[31] which were available in all cohorts. In sensitivity analyses, we also accounted for the following characteristics: (1) adjusted for diabetes mellitus[32]; (2) excluded participants who were receiving thyroid-altering medication (oral corticosteroids, amiodarone, iodine) or anti-fracture medication (bisphosphonates, calcitonin, selective estrogen receptor modulators, parathyroid hormones); (3) limited the analysis to the 8 studies with formal adjudication or those with the most uniform fracture definition; (4) restricted the analysis to participants with repeated measurement of thyroid function to

assess the association with persistent thyroid dysfunction; (5) excluded cohorts with loss to follow-up rates of greater than 5%; (6) excluded cohorts with fracture ascertainment methods other than independent blind assessment or record linkage (eTable 2 in Supplement 1); (7) excluded participants with missing FT_4 levels or abnormal free or total T_3; (8) excluded studies inconsistent with the proportional hazard assumption; (9) excluded studies because of potential publication bias in funnel plots; and (10) applied age-specific TSH reference ranges.[33]

To explore potential sources of heterogeneity, we performed predefined subgroup analyses according to age, sex, and TSH levels. We calculated linear *P* for trend and *P* for interaction for stratified analyses. We used Poisson models to calculate event rates.[34] The proportional hazard assumption was assessed by graphical methods (log-log graphs) and the Schoenfeld test.[35] We excluded cohorts violating the proportional hazard assumption in sensitivity analyses. We visually assessed funnel plots of age- and sex-adjusted estimates and used the Egger test to assess for publication bias.[36]

Results

Among 1371 studies identified in our literature search, 13 prospective cohorts met inclusion criteria (eFigure 1 in Supplement 1). The final sample consisted of 70 298 participants (median age was 64 years; 61.3% women), a median (interquartile range) follow-up of 12.1 (8.3–13.0) years, and a total follow-up of 762 401 person-years (Table). A total of 63 987 (91.0%) of the participants were euthyroid, 4092 (5.8%) had subclinical hypothyroidism, and 2219 (3.2%) had subclinical hyperthyroidism, including 1669 (2.4%) with low but not suppressed TSH (0.10–0.44 mIU/L) and 550 (0.8%) with suppressed TSH (<0.10 mIU/L). We excluded the Nagasaki Adult Health Study[20] from the analysis of subclinical hyperthyroidism because it used first-generation thyrotropin assays.

Incident hip fractures were collected in all cohorts except one,[18] resulting in a study sample of 64 691 participants for the primary outcome. Data were available for any fracture in 28 561 participants from 8 cohorts, for nonspine fractures in 24 155 participants from 8 studies, and for clinical spine fractures in 22 491 participants from 6 cohorts. During follow-up, 2975 (4.6% in 12 studies) participants had an incident hip fracture, 2528 (9.0% in 8 studies) had a fracture in any location, 2018 (8.4% in 8 studies) had a nonspine fracture, and 296 (1.3% in 6 studies) had a spine fracture.

Although study quality was good (see eMethods and eTable 2 in Supplement 1), 2 cohorts did not ascertain fractures with independent blind assessment or record linkage, 5 cohorts did not formally adjudicate fractures, and 2 cohorts had a loss to follow-up of greater than 5%.

Subclinical Hyperthyroidism and Fracture Risk

In age- and sex-adjusted analyses, when compared with euthyroidism, subclinical hyperthyroidism was associated with HRs of 1.36 (95% CI, 1.13–1.64; 6.0 vs 4.9 per 1000 person-years, respectively) for hip fracture, 1.28 (95% CI, 1.06–1.53; 14.4 vs 11.2 per 1000 person-years) for any fracture, 1.16 (95% CI, 0.95–1.41; 9.9 vs 8.1 per 1000 person-years)

for nonspine fracture, and 1.51 (95% CI, 0.93–2.45; 1.8 vs 1.2 per 1000 person-years) for spine fracture (Figure 1). Numbers of fracture events and participants, as well as individual HRs with CIs for each cohort, are described in Figure 1. Two individual studies found that subclinical hyperthyroidism was associated with increased risk for hip fractures (Cardiovascular Health Study[8] and the Sheffield Study[6]). No individual study found a statistically significant association of subclinical hyperthyroidism with the secondary outcomes: any fracture, nonspine fracture, or clinical spine fracture. Although 95% CIs were large in some cohorts, heterogeneity was low for all outcomes (all $\tau^2 \leq 0.01$).

Figure 2 displays stratified analyses for incident hip, any, nonspine, and spine fracture events, comparing subclinical hyperthyroidism vs euthyroidism. Men with subclinical hyperthyroidism had higher HRs than women for all fracture outcomes, without statistically significant interactions except for spine fractures (*P* for interaction ≤.02). Risks did not differ when stratified by age.

Figure 3 displays the association between subclinical hyperthyroidism and the risk of fracture by TSH category. Risks for hip, any, and spine fracture were higher in participants with lower TSH levels. TSH levels of less than 0.10mIU/L were not associated with increased risk of non-spine fracture. The multivariable analysis yielded similar results (eTable 3 in Supplement 1).

Sensitivity analyses excluding participants with missing FT_4, T_3, or those who had been prescribed antiosteoporotic medication; restricting the analysis to studies with formal adjudication or those with the most uniform fracture definition; or excluding studies inconsistent with the proportional hazard assumption (possible publication bias in funnel plots), with a greater than 5% loss to follow-up, with fracture ascertainment methods other than independent blind assessment, or record linkage all yielded similar results (eTables 4–6 in Supplement 1). After excluding participants who had been prescribed thyroid or antithyroid medication at baseline (4%), participants with endogenous subclinical hyperthyroidism had statistically significant increased risk estimates for all fracture outcomes except for nonspine fractures. Although point estimates were similar for persistent thyroid dysfunction, our findings were not statistically significant with larger CIs. Restricting the analysis to 9 cohorts with previously published fracture data generally yielded similar risk estimates (eTable 6 in Supplement 1) without statistically significant interactions, when compared to 4 cohorts with unpublished fracture data. When restricting analyses to 4 cohorts with unpublished fracture data, results were not statistically significant.

Subclinical Hypothyroidism and Fracture Risk

We found no association between subclinical hypothyroid-ism and fracture risks either overall (eFigure 2 in Supplement 1) or in stratified analyses (eTable 7 in Supplement 1), with an HR compared with euthyroid participants of 0.96 (95% CI, 0.83–1.10) for hip fracture, 1.02 (95% CI, 0.89–1.18) for any fracture, 1.06 (95% CI, 0.90–1.24) for nonspine fracture, and 0.96 (95% CI, 0.59–1.55) for spine fracture. Sensitivity analyses did not change results (eTable 8 in Supplement 1).

Treatment With Thyroxine and Fracture Risk

When comparing between participants treated with thyroxine at baseline vs untreated participants regardless of thyroid function, treatment with thyroxine was not associated with any of the fracture outcomes (eTable 9 in Supplement 1).

Discussion

In this analysis of 70 298 individual participants from 13 prospective cohorts, subclinical hyperthyroidism was associated with an increased risk for hip and other fractures, with the highest risks in individuals with suppressed TSH (<0.10 mIU/L) and in those with endogenous subclinical hyperthyroidism. Conversely, our study found no association between subclinical hypothyroidism and fractures. Our pooled data analysis demonstrates that subclinical hyperthyroidism was associated with increased fracture risk and provides insight on defined subgroups.

To our knowledge, no pooled individual participant data analysis has previously assessed the association of subclinical thyroid dysfunction and fracture events. The Cardiovascular Health Study prospectively followed a cohort of 3567 older adults and found that in men, there was an association between increased hip fracture risk and subclinical hyperthyroidism (HR, 3.07; 95% CI, 1.11–8.46), as well as subclinical hypothyroidism (HR, 1.86; 95% CI, 1.09–3.16).[8] Our results confirm the association of subclinical hyperthyroidism with risk of hip fracture. A prospective case-cohort study of 686 women aged 65 years and older found an odds ratio of 4.5 (95% CI 1.3–15.6) for spine fracture, detected in serial radiographs in women with a TSH level 0.10 mIU/L or less, compared with normal TSH levels after a mean follow-up of 3.7 years.[3] Our study also found that endogenous subclinical hyperthyroidism was associated with increased risk of clinically diagnosed spine fractures (HR, 1.74; 95% CI, 1.01–2.99). However, because not all radiographic fractures are clinically diagnosed,[43] it is difficult to directly compare results with the prior study. Although there is some evidence that thyroid hormone level is associated more strongly with changes in cortical than in trabecular bone,[44,45] we did not observe a stronger association with a more cortical (hip) vs a more trabecular (spine) fracture site.

Thyroid function may influence fracture risk through several mechanisms. First, thyroid hormones have been shown to have effects on osteoclasts and osteoblasts, with thyroid status in the upper normal range or excess thyroid hormones leading to accelerated bone turnover with bone loss and increased fracture risk.[4] Second, the association of subclinical hyperthyroidism with increased fracture risk might be mediated by an increased risk of falls[46] through effects on muscle strength and coordination.[41,47] Third, the increase in fracture risk could be related to thyroxine supplementation. In the TEARS study, participants receiving thyroid hormone replacement therapy had a higher rate of fractures when TSH was suppressed, compared with treated euthyroid participants (adjusted HR, 2.02; 95% CI, 1.55–2.62). However, participants with overt thyroid dysfunction might have been included in the TEARS study. FT_4 levels were not measured and the study did not include an untreated control group.[5] Another nested case-control study of more than 120 000 prevalent levothyroxine users showed that levothyroxine use was associated with increased fracture risk when compared with discontinuation of levothyroxine more than 6 months

previously. However, TSH levels were not considered in these analyses.[48] Our results showed an association of subclinical hyperthyroidism with increased risk of all fracture outcomes except nonspine fractures when thyroid medication users (thyroxine and antithyroid medication) were excluded from analyses. These results suggest that endogenous hyperthyroidism is associated with increased fracture risk. Endogenous subclinical hyperthyroidism may be undetected for years because symptoms of subclinical hyperthyroidism are often nonspecific or absent. This phenomenon has the potential to lead to a greater length of time for adverse associations with bone metabolism. Baseline thyroxine use was not associated with increased fracture risk when TSH levels were not taken into account. A possible explanation for this is that patients receiving replacement therapy have more frequent thyroid function tests followed by thyroxine dosage change when overtreatment is detected, and thus do not exhibit a long-standing form of subclinical hyperthyroidism.

Our study has important strengths. First, to our knowledge, this is the largest study of adults with subclinical thyroid dysfunction and prospective follow-up of fracture outcomes. An individual participant data analysis is not subject to potential aggregation bias arising in study-level meta-analyses[49] and is therefore seen as the optimal approach to combining evidence across multiple studies and performing time-to-event analyses.[50] In addition, individual participant data analysis enables use of standardized definitions of predictors and outcomes, and standardized adjustment for confounding factors,[10] thus producing more robust results. We were also able to include 4 cohort studies that have not previously published their data on thyroid dysfunction and fractures (Busselton Health Study,[19] PROSPER Study,[18] InCHIANTI Study,[21] and Nagasaki Adult Health Study[20]), and all prospective cohorts identified through our systematic search agreed to participate, which increased our power to detect potential associations.

Our study has limitations. First, in the majority of cohorts, thyroid function was assessed at baseline only, which is a limitation of most published large cohorts on the risk of subclinical thyroid dysfunction.[12,38] Subclinical hypothyroidism has an annual rate of 2% to 6% for spontaneous progression to overt thyroid dysfunction,[51] while 15% to 65% revert to normal thyroid function over follow-up periods of 1 to 6 years.[52] Subclinical hyperthyroidism similarly progresses to overt disease in 1% to 2% of affected individuals per year.[53,54] In our pooled data, 5.3% of participants with baseline subclinical hyperthyroidism developed overt hyperthyroidism on follow-up thyroid function assessment vs 1.6% of participants when excluding thyroxine use at baseline (endogenous form). A sensitivity analysis, restricted to participants with persistent subclinical thyroid dysfunction using repeated thyroid function measurement in 5 cohorts with available data, yielded similar HRs for hip and any fracture outcomes, with nonstatistically significant results, possibly due to smaller sample sizes. Second, it was not possible to achieve a uniform definition for each fracture type across all cohorts. Sensitivity analyses limited to cohorts with the most uniform fracture definition, however, yielded similar results. Third, we defined subclinical hyperthyroidism by low TSH and normal FT_4 levels because T_3 levels were measured only in 4 cohorts. Consequently, participants with T_3 toxicosis may have been defined as having subclinical hyperthyroidism, but results remained similar in sensitivity analyses excluding participants with abnormal T_3 levels in the cohorts that had this measurement available. Likewise, we may have included

participants with nonthyroidal illness from other cohorts in which T_3 levels were not measured. Fourth, only 8 of 13 studies formally adjudicated fracture outcomes; sensitivity analyses limited to these studies yielded similar results. Fifth, our pooled data contained relatively few young adults and a primarily white population, thus limiting generalizability. Sixth, in spite of the large number of participants, event numbers were low for some outcomes, such as clinical spine fractures, limiting power for subgroup analyses. Seventh, younger participants may have been more likely to experience traumatic fractures and mechanism of injury was not collected in most cohorts. However, fractures in locations not typically associated with osteoporosis or low bone mass density were excluded. Eighth, history of fracture or history of maternal and parental hip fracture were unavailable for most participants or we could not rule out the possibility of residual confounding.

Current guidelines recommend that treatment of subclinical hyperthyroidism should be strongly considered if TSH is persistently lower than 0.1 mIU/L in all individuals aged 65 years or older and that treatment should also be considered if TSH is low but at least 0.1 mIU/L in individuals who are at least 65 years old.[55] Our results from pooling data of all available prospective cohorts, showing increased fracture risk in subclinical hyperthyroidism with even higher risk for participants with TSH levels of less than 0.10 mIU/L, are consistent with these recommendations. Due to the previously mentioned limitations, evidence from observational data should be used with caution in clinical decision making. Some small randomized controlled trials (14–66 participants) have studied the short-term effect (follow-up time of 6–14 months) of subclinical thyroid dysfunction treatment on bone mineral density with conflicting results,[56–59] but no randomized controlled trial has been conducted regarding treatment of subclinical thyroid dysfunction to reduce fracture risk. There are also no studies comparing the relative benefit of treatment of subclinical hyperthyroidism vs treatment with bisphosphonates or other antifracture agents.

Conclusions

Subclinical hyperthyroidism was associated with an increased risk of hip and other fractures, particularly among those with TSH levels lower than 0.10 mIU/L and those with endogenous subclinical hyperthyroidism. Further study is needed to determine whether treating subclinic al hyperthyroidism can prevent fractures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding/Support: This project was supported by grants from the Swiss National Science Foundation (SNSF 320030-138267 and 320030-150025) and partially supported by a grant from the Swiss Heart Foundation (Dr Rodondi). The Cardiovascular Health Study was supported by contracts from the National Heart, Lung, and Blood Institute (NHLBI) (HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086; and grant U01HL080295) with an additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided by the NIA (R01AG023629). The thyroid measurements in the Cardiovascular Health Study were supported by an American Heart Association Grant-in-Aid (Dr Fried). The Health, Aging, and Body Composition Study was supported by the NIA (contract numbers: N01-AG-6-2101, N01-AG-6-2103, N01-AG-6-2106; and grant R01-AG028050); and an NINR grant (R01-NR012459). The NIA funded the Health, Aging, and Body

Composition Study, reviewed the manuscript, and approved its publication. This research was supported in part by the NIA. The EPIC (European Prospective Investigation of Cancer)-Norfolk Study was supported by research grants from the Medical Research Council UK and Cancer Research UK. The Osteoporotic Fractures in Men (MrOS) Study is supported by NIH funding. The following institutes provided support: the NIA, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Center for Advancing Translational Sciences (NCATS), and NIH Roadmap for Medical Research (grant numbers: U01AG027810, U01AG042124, U01AG042139, U01AG042140, U01AG042143, U01AG042145, U01AG042168, U01AR066160, and UL1TR000128). The Nord-Trøndelag Health Study (HUNT Study) is a collaborative effort of the Faculty of Medicine, Norwegian University of Science and Technology; the Norwegian Institute of Public Health; and the Nord-Trøndelag County Council. Thyroid function testing in the HUNT Study was financially supported by Wallac Oy (Turku, Finland). The Leiden 85-plus Study was partly funded by the Dutch Ministry of Health, Welfare and Sports. The original PROSPER study was supported by an unrestricted, investigator-initiated grant from Bristol-Myers Squibb. The Rotterdam Study is funded by Erasmus MC and Erasmus University, Rotterdam, the Netherlands; the Netherlands Organisation for Scientific Research (NWO); the Netherlands Organisation for the Health Research and Development (ZonMw); the Research Institute for Diseases in the Elderly (RIDE); the Ministry of Education, Culture and Science; the Dutch Ministry for Health, Welfare and Sports; the European Commission (DG XII); and the Municipality of Rotterdam. The original OPUS study was supported by sanofi-aventis, Eli Lilly, Novartis, Pfizer, Procter & Gamble Pharmaceuticals, and Roche. Dr Westendorp is supported by the Netherlands Organization for Scientific Research (NGI/NWO 911-03-016). Dr Collet reports receipt of research support from grants from the Swiss National Science Foundation and the Swiss Foundation for Grants in Biology and Medicine (PBLAP3-145870, P3SMP3-155318).

Participating Studies of the Thyroid Studies Collaboration

United States: Cardiovascular Health Study; Health, Aging, and Body Composition Study; and the Osteoporotic Fractures in Men (MrOS) Study. United Kingdom: EPIC-Norfolk Study; and the Sheffield Study. United Kingdom/France/Germany: Osteoporosis and Ultrasound Study (OPUS). Norway: Nord-Trøndelag Health Study (HUNT Study). the Netherlands: Leiden 85-Plus Study; and the Rotterdam Study. the Netherlands/Ireland/Scotland: PROSPER Study. Italy: Invecchiare in Chianti (InCHIANTI) Study. Australia: Busselton Health Study. Japan: Nagasaki Adult Health Study.

Group Information

A full list of principal Cardiovascular Health Study investigators and institutions can be found at CHS-NHLBI.org. The HUNT Research Centre and the Department for Research and Development at Nord-Trøndelag Hospital Trust provided the data for the HUNT Study. The OPUS study was designed and conducted by David M. Reid, MD, FRCPEdin, FRCPLon, Division of Applied Medicine, University of Aberdeen, United Kingdom; Claus C. Glüer, PhD, Universitätsklinikum Schleswig-Holstein, Kiel, Germany; Dieter Felsenberg, MD, PhD, Free University of Berlin, Germany; Christian Roux, MD, PhD, Paris Descartes University, France; and Richard Eastell and Graham R. Williams.

Author Contributions

Drs Blum and Rodondi had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr Rodondi had final responsibility for the decision to submit for publication.

Study concept and design: Blum, Bauer, Westendorp, Khaw, Langhammer, Ferrucci, Gussekloo, Rodondi.

Acquisition, analysis, or interpretation of data: Blum, Bauer, Collet, Fink, Cappola, de Costa, Wirth, Peeters, Åsvold, Elzen, Luben, Imaizumi, Bremner, Gogakos, Eastell,

Kearney, Strotmeyer, Wallace, Hoff, Ceresini, Rivadeneira, Uitterlinden, Stott, Westendorp, Khaw, Langhammer, Ferrucci, Gussekloo, Williams, Walsh, Jüni, Aujesky, Rodondi.

Drafting of the manuscript: Blum, Rodondi.

Critical revision of the manuscript for important intellectual content: Blum, Bauer, Collet, Fink, Cappola, de Costa, Wirth, Peeters, Åsvold, Elzen, Luben, Imaizumi, Bremner, Gogakos, Eastell, Kearney, Strotmeyer, Wallace, Hoff, Ceresini, Rivadeneira, Uitterlinden, Stott, Westendorp, Khaw, Langhammer, Ferrucci, Gussekloo, Williams, Walsh, Jüni, Aujesky.

Statistical analysis: Blum, de Costa, Gogakos, Jüni, Rodondi.

Obtained funding: Peeters, Ceresini, Uitterlinden, Stott, Westendorp, Khaw, Gussekloo, Williams, Walsh, Rodondi.

Administrative, technical, or material support: Blum, Peeters, Elzen, Luben, Kearney, Wallace, Uitterlinden, Khaw, Langhammer, Gussekloo, Aujesky, Rodondi.

Study supervision: Bauer, Hoff, Rivadeneira, Uitterlinden, Westendorp, Ferrucci, Jüni, Rodondi.

Conflict of Interest Disclosures

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Collet reports receipt of grants from the Swiss National Science Foundation during the conduct of the study. Dr Peeters reports receipt of personal fees from Genzyme B.V. outside of the submitted work. Dr Eastell reports receipt of grants from Amgen, AstraZeneca, Immunodiagnostic Systems, Canadian Institutes of Health Research, National Osteoporosis Society, Arthritis Research United Kingdom/Medical Research Council Centre of Excellence in Musculoskeletal Ageing Research, National Institute for Health Research, Cancer Research UK, and Medical Research Council/AstraZeneca Mechanisms of Disease Call during the conduct of the study; and personal fees from Novartis, Roche, Alexion, Otsuka, Teijan Pharma Limited, Institute of Biomedical Science, Merck, Amgen, Eli Lilly, Foundation for the National Institutes of Health (NIH), Endocrine Society, Johnson & Johnson, SPD Development, Fonterra Brands, Janssen Research, Ono Pharma, Immunodiagnostic Systems, Alere (Unipath), Chronos, GlaxoSmithKline Nutrition, Radius Health, European Calcified Tissue Society, Efficacy and Mechanism Evaluation Board of the Medical Research Council, and the International Osteoporosis Foundation Committee of Scientific Advisors, all outside of the submitted work. Dr Strotmeyer reports receipt of grants from the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR), and the University of Pittsburgh Claude D. Pepper Older Americans Independence Center during the conduct of the study, all outside of the submitted work. Dr Rodondi reports receipt of funding for a randomized controlled trial on subclinical hypothyroidism (TRUST trial) from the European Commission FP7-HEALTH-2011, Specific Programme “ Cooperation” – Theme “ Health” Investigator-driven clinical trials for

therapeutic interventions in elderly populations (proposal: 278148-2). No other conflicts were reported.

Role of the Funder/Sponsor

None of the sponsors had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication; except: (1) The NIA, which funded the Health, Aging, and Body Composition Study, reviewed the manuscript and approved its publication; (2) the Cardiovascular Health Study, which reviewed this manuscript for scientific content and consistency of data interpretation with previous Cardiovascular Health Study publications; and (3) the Radiation Effects Research Foundation, which funded the Nagasaki Adult Health Study and reviewed the manuscript and approved its publication.

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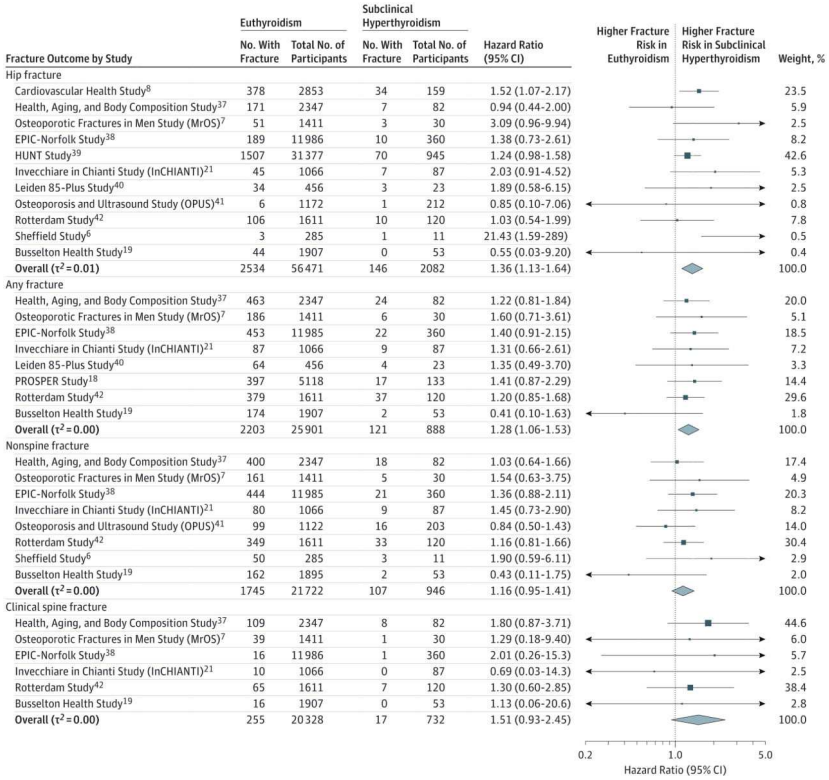

Figure 1. Association Between Subclinical Hyperthyroidism and Fracture Risk

Hazard ratios (HRs) were adjusted for age and sex. Data marker sizes are proportional to the inverse of the variance of the HRs. Error bars indicate 95% CIs. Not every outcome was available for each study. Calculations of τ^2 were used to measure heterogeneity in effect estimates across cohorts, with a prespecified τ^2 (≤0.04) indicating low heterogeneity and greater than 0.04 to 0.36 indicating moderate heterogeneity.

Fracture Outcome by Age and Sex	Euthyroidism No. With Fracture	Euthyroidism Total No. of Participants	Subclinical Hyperthyroidism No. With Fracture	Subclinical Hyperthyroidism Total No. of Participants	Hazard Ratio (95% CI)	*P* for Interaction
Hip fracture[a]						
Sex						
Men	606	21854	22	468	1.92 (1.26-2.94)	.09
Women	1928	34617	124	1614	1.29 (1.08-1.55)	
Age, y[b]						
<75	1360	47540	78	1646	1.54 (1.22-1.93)	.18
≥75	1162	8462	67	431	1.22 (0.95-1.56)	
Overall	2534	56471	146	2082	1.36 (1.13-1.64)	
Any fracture[c]						
Sex						
Men	796	13091	32	327	1.69 (1.18-2.41)	.12
Women	1407	12810	89	561	1.21 (0.98-1.51)	
Age, y[b]						
<75	1363	20067	69	649	1.33 (1.04-1.69)	.72
≥75	840	5834	52	239	1.24 (0.93-1.65)	
Overall	2203	25901	121	888	1.28 (1.06-1.53)	
Nonspine fracture[d]						
Sex						
Men	592	10326	24	282	1.53 (1.01-2.31)	.17
Women	1153	11396	83	664	1.10 (0.88-1.37)	
Age, y[b]						
<75	1218	18707	69	766	1.17 (0.85-1.59)	.74
≥75	527	2847	36	175	1.08 (0.77-1.53)	
Overall	1745	21722	107	946	1.16 (0.95-1.41)	
Spine fracture[e]						
Sex						
Men	106	10332	7	282	3.61 (1.76-7.41)	.02
Women	149	9996	10	450	1.17 (0.63-2.19)	
Age, y[b]						
<75	167	17476	9	581	1.64 (0.87-3.10)	.82
≥75	86	2732	8	148	1.83 (0.89-3.79)	
Overall	255	20328	17	732	1.51 (0.93-2.45)	

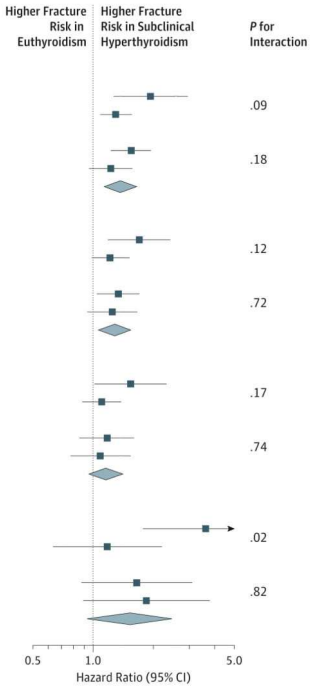

Figure 2. Stratified Analyses for the Association Between Subclinical Hyperthyroidism and Fracture Risk

All hazard ratios (HRs) were age and sex adjusted. Error bars indicate 95% CIs. The multivariable analysis yielded similar results (eTable 3 in Supplement 1).

[a]The PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) Study was not included because follow-up data were only available for any fracture.

[b]These HRs were adjusted for sex and age as a continuous variable to avoid residual confounding within age strata.

[c]The HUNT (Nord-Trøndelag Health Study), Cardiovascular Health Study, Sheffield, and OPUS (Osteoporosis and Ultrasound Study) studies were not included because follow-up data for any fracture were not available.

[d]The HUNT, Cardiovascular Health Study, Leiden 85-Plus, and PROSPER studies were not included because follow-up data for nonspine fractures were not available.

[e]The HUNT, Cardiovascular Health Study, Leiden 85-Plus, Sheffield, OPUS, and PROSPER studies were not included because follow-up data for spine fractures were not available.

Fracture Outcome by Thyroid-Stimulating Hormone Levels, mIU/L	Euthyroidism		Subclinical Hyperthyroidism		Hazard Ratio (95% CI)	P for Trend
	No. With Fracture	Total No. of Participants	No. With Fracture	Total No. of Participants		
Hip fracture[a]						
0.45-4.49	2534	56471			1 [Reference]	
0.10-0.44			99	1568	1.34 (1.01-1.77)	.001
<0.10			47	510	1.61 (1.21-2.15)	
Any fracture[b]						
0.45-4.49	2203	25901			1 [Reference]	
0.10-0.44			77	676	1.10 (0.87-1.38)	<.001
<0.10			44	212	1.98 (1.41-2.78)	
Nonspine fracture[c]						
0.45-4.49	1745	21722			1 [Reference]	
0.10-0.44			74	757	1.02 (0.81-1.29)	.07
<0.10			32	185	1.61 (0.96-2.71)	
Spine fracture[d]						
0.45-4.49	255	20328			1 [Reference]	
0.10-0.44			9	566	1.12 (0.59-2.13)	<.001
<0.10			8	162	3.57 (1.88-6.78)	

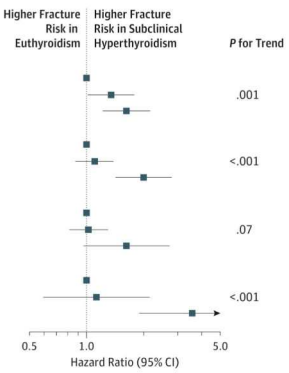

Figure 3. Association Between Subclinical Hyperthyroidism and Fracture Risk Categorized by Thyroid-Stimulating Hormone Level

All hazard ratios (HRs) were age and sex adjusted. Error bars indicate 95% CIs. The multivariable analysis yielded similar results (eTable 3 in Supplement 1).

[a]The PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) Study was not included because follow-up data were only available for any fracture.

[b]The HUNT (Nord-Trøndelag Health Study), Cardiovascular Health Study, Sheffield, and OPUS (Osteoporosis and Ultrasound Study) studies were not included because follow-up data for any fracture were not available.

[c]The HUNT, Cardiovascular Health Study, Leiden 85-Plus, and PROSPER studies were not included because follow-up data for nonspine fractures were not available.

[d]The HUNT, Cardiovascular Health Study, Leiden 85-Plus, Sheffield, OPUS, and PROSPER studies were not included because follow-up data for spine fractures were not available.

Table

Characteristics of Individuals in Included Studies (N=70298)

ation)	Description of Study Sample	No. of Participants	Age, Median (Range), y[a]	Women, No. (%)	Subclinical Thyroid Dysfunction, No. (%)[b]		Thyroid Medication Users, No. (%)		Follow-up[e]		
					Hypothyroidism	Hyperthyroidism	At Baseline	During Follow-up	Start, y	Duration, Median (IQR), y	Person-Years
ular Health ted States)	Community-dwelling adults with Medicare eligibility in 4 communities	3555	71 (65–100)	2185 (61.5)	543 (15.3)	159 (4.5)	295 (8.3)[c]	629 (17.7)	1989–1990	12.8 (7.5–18.8)	45 160
C Study,[37] (United	Community-dwelling adults aged 70–79 y with Medicare eligibility in 2 communities	2764	74 (69–81)	1407 (50.9)	335 (12.1)	82 (3.0)	267 (9.7)[c]	383 (13.9)	1997	12.8 (8.1–13.2)	29 292
c Fractures in Men OS),[7] (United States)	Community-dwelling men aged ≥65 y in 6 clinical centers	1588	73 (65–99)	0	147 (9.3)	30 (1.9)	121 (7.6)[c]	152 (9.6)[d]	2000–2002	11.1 (8.0–11.8)	15 133
olk Study,[38] (England)	Adults aged 45–79 y	13 066	58 (40–78)	7104 (54.4)	720 (5.5)	360 (2.8)	439 (3.4)	NA[d]	1995–1998	12.4 (11.6–13.3)	155 661
dy,[39] (Norway)[f]	Adults	33 646	57 (19–99)	22 988 (68.3)	1313 (3.9)	945 (2.8)	1576 (4.7)[c]	NA[d]	1995–1997	12.2 (11.6–12.8)	369 413
I Study,[21] (Italy)	Community-dwelling adults aged ≥65 y	1186	71 (21–102)	664 (56.0)	33 (2.8)	87 (7.3)	28 (2.4)	48 (4.0)[d]	1998	9.1 (7.2–9.3)	9393
Plus Study,[40] (the)	Adults aged 85 y	514	85	336 (65.4)	35 (6.8)	23 (4.5)	17 (3.3)	29 (5.6)	1997–1999	4.9 (2.2–8.2)	2736
y,[41] (Germany, gland)[g]	Women aged 20–80 y	1433	63 (20–80)	1433 (100.0)	12 (0.8)	216 (15.1)	0	NA	1999–2001	6.0 (5.8–6.3)	8556
Study,[18] (the , Ireland, Scotland)	Older community-dwelling adults at high cardiovascular risk	5563	75 (69–83)	2824 (50.8)	306 (5.5)	133 (2.4)	184 (3.3)	252 (4.5)[d]	1997–1999	3.2 (3.0–3.5)	17 162
Study,[42] (the)	Adults aged ≥55 y	1838	69 (55–93)	1127 (61.3)	107 (5.8)	120 (6.5)	42 (2.3)[c]	NA[d]	1989–1992	15.2 (10.2–16.2)	24 031
udy,[6] (England)	Women aged 50–85 y	334	63 (50–86)	334 (100.0)	32 (9.6)	11 (3.3)	5 (1.5)	21 (6.3)[d]	1990–1991	10.0 (5.3–10.1)	2597

Study (Location)	Description of Study Sample	No. of Participants	Age, Median (Range), y[a]	Women, No. (%)	Subclinical Thyroid Dysfunction, No. (%)[b]		Thyroid Medication Users, No. (%)		Blum et al	
					Hypothyroidism	Hyperthyroidism	At Baseline	During Follow-up	Stanl, y	D Med
Busselton Health Study,[19] (Australia)	Adults	2049	51 (18–90)	1006 (49.1)	89 (4.3)	53 (2.6)	19 (0.9)	34 (1.7)	1981	20.0
Nagasaki Adult Health Study,[20] (Japan)	Atomic bomb survivors	2762	57 (38–92)	1686 (61.0)	420 (15.2)	NA[h]	39 (1.4)	6 (0.2)[d]	1984–1987	20.2
Overall	13 Cohorts	70 298	64 (18–102)	43 094 (61.3)	4092 (5.8)	2219 (3.2)	3032 (4.3)	1554 (9.0)	1981–2002	12.1

Abbreviations: EPIC, European Prospective Investigation of Cancer; HUNT, Nord-Trøndelag Health Study; InCHIANTI, Invecchiare in Chianti Study; IQR, interquartile range; NA, not available; OPUS, Osteoporosis and Ultrasound Study; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; TSH, thyroid-stimulating hormone.

[a] Participants younger than 18 years were excluded.

[b] We used a common definition of subclinical thyroid dysfunction, whereas TSH cutoff values varied among the previous reports from different cohorts, resulting in different numbers from previous reports.

[c] Data on baseline thyroid medication use (thyroxine, antithyroid drugs) were unavailable for 273 participants of the HUNT Study, 1 participant of the Cardiovascular Health Study, 64 participants of the Osteoporotic Fractures in Men Study, 8 participants of the Health ABC Study, and 1 participant of the Rotterdam Study.

[d] Data on thyroid medication use during follow-up were unavailable for 294 participants of the Osteoporotic Fractures in Men Study, 119 participants of the Invecchiare in Chianti Study, 2509 participants of the Nagasaki Adult Health Study, 56 participants of the Sheffield Study, and for all participants of the HUNT Study, EPIC-Norfolk Study, Rotterdam Study, and Osteoporosis and Ultrasound Study.

[e] For all cohorts, we used the maximum follow-up data available (calculated as time to first hip or any fracture or censor date/death), which might differ from previous reports for some cohorts.

[f] The sample included for the original article of the HUNT study used several inclusion/exclusion criteria that differed from those used here (such as excluding participants younger than 40 years and those with previous fractures or previous thyroid disease), resulting in different numbers of participants.

[g] The original OPUS was a population-based study with no exclusions. The sample included here is the thyroid hormone substudy of OPUS, which excluded thyroid medication users.

[h] Twenty-one participants with TSH<0.45mIU/L and free thyroxine within the normal range were excluded from the Nagasaki cohort due to the use of a first-generation TSH assay that is not sensitive enough to detect subclinical hyperthyroidism.