Subclinical Thyroid Dysfunction and Fracture Risk: A Meta-Analysis

Manuel R. Blum, MD (manuel.blum@insel.ch) [1]; Douglas C. Bauer, MD (dbauer@psg.ucsf.edu) [2]; Tinh-Hai Collet, MD (tinh-hai.collet@chuv.ch) [3]; Howard A. Fink, MD, MPH (howard.fink@va.gov) [4,5]; Anne R. Cappola, MD, ScM (acappola@mail.med.upenn.edu) [6]; Bruno R. da Costa, PhD (bdacosta@fiu.edu) [7]; Christina D. Wirth, MD (christina.wirth@insel.ch) [1]; Robin P. Peeters, MD, PhD (r.peeters@erasmusmc.nl) [8,9]; Bjørn O. Åsvold, MD, PhD (bjorn.o.asvold@ntnu.no) [10,11]; Wendy P. J. den Elzen, PhD (w.p.j.den_elzen@lumc.nl) [12]; Robert N. Luben, PhD (robert.luben@phpc.cam.ac.uk) [13]; Misa Imaizumi, MD, PhD (misaima@rerf.or.jp) [14]; Alexandra P. Bremner, PhD (alexandra.bremner@uwa.edu.au) [15]; Apostolos Gogakos, MD, PhD (a.gogakos@imperial.ac.uk) [16]; Richard Eastell, MD (r.eastell@sheffield.ac.uk) [17]; Patricia M. Kearney, MD, PhD, MPH (patricia.kearney@ucc.ie) [18]; Elsa S. Strotmeyer, MD, PhD (strotmeyere@edc.pitt.edu) [19]; Erin R. Wallace, PhD (wallace8@u.washington.edu) [20]; Mari Hoff, MD, PhD (mari.hoff@ntnu.no) [10,21]; Graziano Ceresini, MD, PhD (graziano.ceresini@unipr.it) [22]; Fernando Rivadeneira, MD, PhD (f.rivadeneira@erasmusmc.nl) [8,9]; André G. Uitterlinden, PhD (a.g.uitterlinden@erasmusmc.nl) [8,9]; David J. Stott, MD, PhD (David.J.Stott@glasgow.ac.uk) [23]; Rudi G. J. Westendorp, MD, PhD (westendorp@sund.ku.dk) [24]; Kay-Tee Khaw, MD (kk101@medschl.cam.ac.uk) [13]; Arnuf Langhammer, MD, PhD (arnulf.langhammer@ntnu.no) [10]; Luigi Ferrucci, MD, PhD (ferruccilu@mail.nih.gov) [25]; Jacobijn Gussekloo, MD, PhD (j.gussekloo@lumc.nl) [12]; Graham R. Williams, MBBS, PhD (graham.williams@imperial.ac.uk) [16]; John P. Walsh, MBBS, PhD (john.walsh@health.wa.gov.au) [26,27]; Peter Jüni, MD (juni@ispm.unibe.ch) [28]; Drahomir Aujesky, MD, MSc (drahomir.aujesky@insel.ch) [1];

Nicolas Rodondi, MD, MAS (nicolas.rodondi@insel.ch) [1] for the Thyroid Studies Collaboration

Affiliations

[1] Department of General Internal Medicine, Inselspital, Bern University Hospital, Bern, Switzerland; [2] Departments of Medicine and Epidemiology & Biostatistics, University of California, San Francisco, CA, United States; [3] Service of Endocrinology, Diabetes and Metabolism, University Hospital of Lausanne, Lausanne, Switzerland; [4] Department of Medicine, University of Minnesota School of Medicine, Minneapolis, MN, United States; [5] Geriatric Research Education & Clinical Center, VA Medical Center, Minneapolis, MN, United States; [6] University of Pennsylvania School of Medicine, Philadelphia, PA, United States; [7] Department of Physical Therapy, Nicole Wertheim College of Nursing & Health Science, Florida International University, Miami, FL, United States; [8] Department of Internal Medicine, Erasmus Medical Center, Rotterdam, Netherlands; [9] Department of Epidemiology, Erasmus Medical Center, Rotterdam, Netherlands; [10] Department of Public Health and General Practice, Norwegian University of Science and Technology, Trondheim, Norway; [11] Department of Endocrinology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway; [12] Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, Netherlands; [13] Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom; [14] Radiation Effects Research Foundation, Nagasaki, Japan; [15] School of Population Health, University of Western Australia, Crawley, WA, Australia; [16] Department of Medicine, Imperial College London, London, United Kingdom; [17] Department of Human Metabolism, University of Sheffield, Sheffield, United Kingdom; [18] Department of Epidemiology and Public Health, University College Cork, Cork, Ireland; [19] Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA, United

States; [20] Cardiovascular Health Research Unit, University of Washington, Seattle, WA, United States; [21] Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway; [22] Department of Clinical and Experimental Medicine, Geriatric Endocrine Unit, University Hospital of Parma, Parma, Italy; [23] Institute of Cardiovascular and Medical Sciences, University of Glasgow, United Kingdom; [24] Department of Public Health, University of Copenhagen, Copenhagen, Denmark; [25] National Institute on Aging, National Institutes of Health, Baltimore, MD, United States; [26] School of Medicine and Pharmacology, University of Western Australia, Crawley, WA, Australia; [27] Department of Endocrinology & Diabetes, Sir Charles Gairdner Hospital, Nedlands, WA, Australia; [28] Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

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Corresponding author

Nicolas Rodondi, MD, MAS, Department of General Internal Medicine, Inselspital, University of Bern, 3010 Bern, Switzerland; Email: Nicolas.Rodondi@insel.ch, Phone: +41 31 632 41 63, Fax: +41 31 632 88 85

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, any, non-spine and spine 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. Euthyroidism was defined as thyrotropin (TSH) =0.45-4.49mIU/L, subclinical hyperthyroidism as TSH<0.45mIU/L and subclinical hypothyroidism as TSH≥4.50-19.99mIU/L with normal thyroxine concentrations.

Main Outcome Measures

The primary outcome was hip fracture. Any fracture, non-spine fracture, 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 (9.0%; 8 studies), non-spine fracture in 2018 (8.4%; 8 studies) and spine fracture in 296 (1.3%; 6 studies). In age- and sex-adjusted analyses, the hazard ratios (HR) for subclinical hyperthyroidism vs. euthyroidism were 1.36 (95% confidence interval 1.13-1.64; 146 events in 2082 participants vs. 2534/56,471) for hip fracture, 1.28 (1.06-1.53; 121/888 vs. 2203/25,901) for any fracture, 1.16 (0.95-1.41; 107/946 vs. 1745/21,722) for non-spine fracture and 1.51 (0.93-2.45; 17/732 vs. 255/20,328) for spine fracture. Lower TSH was associated with higher fracture rates, with HR for TSH<0.10mIU/L of 1.61 (1.21-2.15; 47/510 participants) for hip, 1.98 (1.41-2.78; 44/212) for any, 1.61 (0.96-2.71; 32/185) for non-spine and 3.57 (1.88-6.78; 8/162) for spine fracture. Risks were similar after adjustment for other fracture risk factors. Endogenous subclinical hyperthyroidism (excluding thyroid medication users) was associated with HRs of 1.52 (1.19-1.93) for hip, 1.42 (1.16-1.74) for any, and 1.74 (1.01-2.99) for spine fractures. 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<0.10mIU/L and those with endogenous subclinical hyperthyroidism. Further study is needed to determine whether treating subclinical hyperthyroidism can prevent fractures.

Abstract Word count

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Keywords

Subclinical Thyroid Dysfunction, Fractures, Hip, Prospective Studies, Cohort Studies

Introduction

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 TSH with normal free thyroxine, could also be associated with increased fracture risk and bone loss[2-4].

Data on the association between subclinical thyroid dysfunction and fracture risk are conflicting in prospective cohort studies, due to 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 different TSH cut-offs to define 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 non-spine, clinical spine, and fractures of any location. This approach allows exploration of the relationship of age, gender, 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 free T4 (FT4) levels[12] 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, anti-thyroid 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 through 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 on 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 TSH 0.45-4.49 mIU/L. Subclinical hyperthyroidism was defined as TSH <0.45 mIU/L with normal FT4 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 TSH 4.5-19.99 mIU/L with normal FT4 levels. Participants with a missing FT4 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)[22]. Cohorts using first-generation TSH assays were excluded from analyses of subclinical hyperthyroidism, because of insufficient sensitivity of first generation thyroid assays[23]. Due to greater inter-method variation, we used cohort-specific cut-offs for FT4 and T3 levels (eTable 1). We performed a sensitivity analysis on persistent thyroid dysfunction using repeated TSH and FT4 measurements (available in 5 cohorts, follow-up duration in eTable 5). 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 FT4 levels, or abnormal total or free T3 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, non-spine, and clinical spine fractures. We standardized outcome definitions (eTable 1). Incident hip fractures typically included fractures of femoral neck, pertrochanteric, and subtrochanteric fractures, excluding pathologic and peri-prosthetic fractures. Incident non-spine fractures were defined as hip or any other non-pathologic fracture excluding the spine, and excluding fractures of skull/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 as these usually occur due to high-energy 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 non-spine or clinically diagnosed spine fracture. Cohorts with fracture data only for parts of the skeleton, such one 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, eMethods). 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 two-step approach, first analyzing the association of subclinical thyroid dysfunction with outcomes using separate Cox proportional hazard models for each cohort (Stata 12.1, StataCorp, College Station, TX, USA), 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 (HR) and 95% confidence intervals (CI) (SAS 9.3, SAS Institute Inc., Cary, NC, USA). Strata with less than six participants per cohort were excluded from pooling due to unreliable estimates. We summarized results using forest plots (Review Manager 5.3.3, Nordic Cochrane Centre, Copenhagen, Denmark). We calculated the variance estimate τ^2 (tau-squared) as a measure of heterogeneity in estimates across cohorts. A $\tau^2 \leq 0.04$ was pre-specified to represent low, >0.04–0.36 moderate, and ≥0.36 high heterogeneity[29]. P values <0.05 were regarded as significant, and testing was two-sided.

Primary analyses were adjusted for age and gender, and then for other known risk factors for fractures, as some might be potential mediators (e.g. 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[30] and smoking status[31], which were available in all cohorts. In sensitivity analyses, we also (1) adjusted for diabetes mellitus[32], (2) excluded participants on thyroid-altering medication (oral corticosteroids, amiodarone, iodine), (3) excluded participants on anti-fracture medication (bisphosphonates, calcitonin, selective estrogen receptor modulator, parathyroid hormone), (4) limited the analysis to the eight studies with formal adjudication or those with the most uniform fracture

236 definition, (5) restricted the analysis to participants with repeated thyroid function
237 measurement to assess the association with persistent thyroid dysfunction, (6)
238 excluded cohorts with loss to follow-up rates >5% and/or fracture ascertainment
239 methods other than independent blind assessment or record linkage (eTable 2), (7)
240 excluded participants with missing FT4 levels or abnormal free/total T3, (8) excluded
241 studies inconsistent with the proportional hazard assumption, (9) excluded studies
242 because of potential publication bias in funnel plots, and (10) applied age-specific TSH
243 reference ranges[33].

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

Results

Among 1371 studies identified in our literature search, 13 prospective cohorts met inclusion criteria (eFigure 1). The final sample consisted of 70,298 participants (median age 64 years, 61.3% women), a median follow-up of 12.1 years, and a total follow-up of 762,401 person-years (Table 1). 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 the 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 eight cohorts, for non-spine fractures in 24,155 participants from eight studies, and for clinical spine fractures in 22,491 participants from six cohorts. During follow-up, 2975 (4.6% in 12 studies) participants had an incident hip fracture, 2528 (9.0% in eight studies) a fracture in any location, 2018 (8.4% in eight studies) a non-spine fracture and 296 (1.3% in six studies) a spine fracture.

Study quality was good (eTable 2). Two cohorts had a loss to follow-up >5% and two cohorts did not ascertain fractures with independent blind assessment or record linkage. Five cohorts did not formally adjudicate fractures.

Subclinical hyperthyroidism and fracture risk

In age- and sex-adjusted analyses, compared to euthyroidism, subclinical hyperthyroidism was associated with hazard ratios of 1.36 (95% confidence interval (95%CI) 1.13-1.64; 6.0 vs. 4.9/1000 person-years, respectively) for hip fracture, 1.28 (1.06-1.53; 14.4 vs. 11.2/1000 person-years) for any fracture, 1.16 (0.95-1.41; 9.9 vs.

8.1/1000 person-years) for non-spine fracture, and 1.51 (0.93-2.45; 1.8 vs. 1.2/1000 person-years) for spine fracture (Figure 1). Numbers of fracture events and participants, as well as individual hazard ratios with confidence intervals 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 and the Sheffield study). No individual study found a statistically significant association of subclinical hyperthyroidism with any, non-spine or clinical spine fracture. Although confidence intervals 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, non-spine, 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 ≤ 0.02). 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 < 0.10mIU/L were not associated with increased risk of non-spine fracture. The multivariable analysis yielded similar results (eTable 3).

Sensitivity analyses excluding participants with missing FT4, T3 or those on anti-osteoporotic medication, restricting the analysis to studies with formal adjudication, those with the most uniform fracture definition, or excluding studies inconsistent with the proportional hazard assumption (possible publication bias in funnel plots), with >5% loss to follow-up, with fracture ascertainment methods other than independent blind assessment or record linkage all yielded similar results (eTables 4-6). After excluding participants who used thyroid or anti-thyroid medication at baseline (4%), participants with endogenous subclinical hyperthyroidism had statistically significant increased risk

estimates for all fracture outcomes except for non-spine fractures. Although point estimates were similar for persistent thyroid dysfunction, our findings were non-statistically significant with larger confidence intervals, likely due to dataavailable only in five cohorts (n=25,497 participants, eTable 5). Restricting the analysis to nine cohorts with previously published fracture data generally yielded similar risk estimates (eTable 6), without statistically significant interactions compared to four cohorts with unpublished fracture data. When restricting analyses to four cohorts with unpublished fracture data, results were non-statistically significant.

Subclinical hypothyroidism and fracture risk

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

Treatment with thyroxine and fracture risk

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

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 those with endogenous subclinical hyperthyroidism. Conversely, our study found no association between subclinical hypothyroidism and fractures. Our pooled data analysis demonstrates that subclinical hyperthyroidism is associated with increased fracture risk and provides insight on defined sub-groups.

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 subclinical hyperthyroidism and hypothyroidism were associated with increased hip fracture risk in men, with HRs 3.07 (95%CI 1.11-8.46) and 1.86 (95%CI 1.09-3.16), respectively[8]. Our results confirm the association of subclinical hyperthyroidism with hip fracture risk. A prospective case-cohort study of 686 women aged over 65 years found an odds ratio of 4.5 (95%CI 1.3-15.6) for spine fracture detected in serial radiographs in women with TSH ≤0.10 mIU/L 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, since not all radiographic fractures are clinically diagnosed[37], it is difficult to directly compare results with the prior study. Although there is some evidence that thyroid hormone is associated more strongly with changes in cortical than in trabecular bone[38,39], we did not observe a stronger association with a more cortical (hip) vs. more trabecular (spine) fracture site.

345 Thyroid function may influence fracture risk through several mechanisms. First, thyroid
346 hormones have been shown to have effects on osteoclasts and osteoblasts, with
347 thyroid status in the upper normal range or excess thyroid hormones leading to
348 accelerated bone turnover with bone loss and increased fracture risk[4]. Second, the
349 association of subclinical hyperthyroidism with increased fracture risk might be
350 mediated by an increased risk of falls[40] through effects on muscle strength and
351 coordination[41,42]. Third, the increase in fracture risk could be related to thyroxine
352 supplementation. In the TEARS study, participants on thyroid hormone replacement
353 had a higher rate of fractures when TSH was suppressed compared with treated
354 euthyroid participants (adjusted HR 2.02; 95%CI 1.55-2.62). However, participants with
355 overt thyroid dysfunction might have been included in the TEARS Study. FT4 levels
356 were not measured and the study did not include an untreated control group[5]. Another
357 nested case-control study of >120,000 prevalent levothyroxine users showed that
358 levothyroxine use was associated with increased fracture risk compared to
359 discontinuation of levothyroxine more than six months previously. However, TSH
360 levels were not considered in these analyses[43]. Our results showed an association of
361 subclinical hyperthyroidism with increased risk of all fracture outcomes except non-
362 spine fractures, when thyroid medication users (thyroxine and anti-thyroid medication)
363 were excluded from analyses. These results suggest that endogenous hyperthyroidism
364 is associated with increased fracture risk. Endogenous subclinical hyperthyroidism may
365 be undetected for years because symptoms of subclinical hyperthyroidism are often
366 non-specific or absent. This phenomenon has the potential to lead to a greater length
367 of time for adverse associations with bone metabolism. Baseline thyroxine use was not
368 associated with increased fracture risk when TSH levels were not taken into account. A
369 possible explanation for this is that patients on replacement therapy have more
370 frequent thyroid function tests followed by thyroxine dosage change when

371 overtreatment is detected, and thus do not exhibit a long-standing form of subclinical
372 hyperthyroidism.

373 Our study has important strengths. First, to our knowledge this is the largest study of
374 adults with subclinical thyroid dysfunction and prospective follow-up of fracture
375 outcomes. An individual participant data analysis is not subject to potential aggregation
376 bias arising in study-level meta-analyses[44] and is therefore seen as the optimal
377 approach to combining evidence across multiple studies and performing time-to-event
378 analyses[45]. In addition, individual participant data analysis enables use of standardized
379 definitions of predictors and outcomes, and standardized adjustment for confounding
380 factors[10], thus producing more robust results. We were also able to include four cohort
381 studies that have not previously published their data on thyroid dysfunction and
382 fractures (Busselton Health Study[19], PROSPER Study[18], InCHIANTI Study[21] and
383 Nagasaki Adult Health Study[20]), and all prospective cohorts identified through our
384 systematic search agreed to participate, which increased our power to detect potential
385 associations.

386 Our study has limitations. First, in the majority of cohorts, thyroid function was
387 assessed at baseline only, which is a limitation of most published large cohorts on the
388 risk of subclinical thyroid dysfunction[12,46]. Subclinical hypothyroidism has an annual
389 rate of 2-6% for spontaneous progression to overt thyroid dysfunction[47], while 15 to
390 65% revert to normal thyroid function over follow-up periods of one to six years[48].
391 Subclinical hyperthyroidism similarly progresses to overt disease in 1-2% of affected
392 individuals per year[49,50]. In our pooled data, 5.3% of participants with baseline
393 subclinical hyperthyroidism developed overt hyperthyroidism on follow-up thyroid
394 function assessment, and 1.6% of participants when excluding thyroxine use at
395 baseline (endogenous form). A sensitivity analysis restricted to participants with
396 persistent subclinical thyroid dysfunction using repeated thyroid function measurement

in five cohorts with available data yielded similar HRs for hip and any fracture outcomes, with non-statistically 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 FT4 levels, as T3 levels were measured only in four cohorts. Consequently, participants with T3 toxicosis may have been defined as having subclinical hyperthyroidism, but results remained similar in sensitivity analyses excluding participants with abnormal T3 levels in the cohorts that had this measurement available. Likewise, we may have included participants with non-thyroidal illness from other cohorts in which T3 levels were not measured. Fourth, only eight 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 sub-group 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/low bone mass density were excluded. Eighth, history of fracture or history of maternal/parental hip fracture were unavailable for most participants and 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 <0.1 mIU/L in all individuals ≥65 years old, and that treatment should also be considered if TSH is low but ≥0.1 mIU/L in individuals ≥65 years old[51]. 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 <0.10 mIU/L, are consistent with these recommendations. Due to the above-mentioned limitations, evidence from observational data should be used with caution in clinical decision-making. Some small randomized controlled trials (RCT) (N=14-66) 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[52-55], but no RCT has been conducted on treating 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 anti-fracture agents.

Conclusions

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

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Drs Blum and Rodondi had full access to all 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.

Participating Studies of the Thyroid Studies Collaboration

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

Author Contributions

Study concept and design: Rodondi, Bauer

Acquisition of data: Rodondi, Gussekloo, Bauer, Cappola, Ceresini, Åsvold, Khaw, Langhammer, Westendorp, Walsh, Williams, Eastell, Imaizumi, Peeters, Wirth

Analysis and interpretation of data: Blum, Bauer, da Costa, Jüni, Rodondi

Drafting of the manuscript: Blum, Rodondi

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

Statistical analysis: Blum, da Costa, Bauer, Jüni, Rodondi.

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Figure 1. Forest plots of the association between subclinical hyperthyroidism and the risk of fractures

Hip, non-spine, spine and any fractures in subclinical hyperthyroidism vs. euthyroidism. Age and sex-adjusted hazard ratios (HR) and their 95% confidence intervals (CI) are represented by squares or diamonds. The sizes of the squares are proportional to the inverse of the variance of the HR. Not every outcome was available for each study. τ^2 measures heterogeneity in effect estimates across cohorts, with a pre-specified τ^2 of ≤0.04 representing low heterogeneity and >0.04 to <0.36 representing moderate heterogeneity. Abbreviations: EPIC: European Prospective Investigation of Cancer. HUNT: Nord-Trøndelag Health Study.

751 **Figure 2. Stratified analyses for the association between subclinical hyperthyroidism and the risk of**
752 **fractures**

753 *Abbreviations*: CI, confidence interval; HR, hazard ratio; TSH, thyroid-stimulating hormone

754 [a] The PROSPER study was not included because follow-up data were only available for any fracture

755 [b] The HUNT, Cardiovascular Health Study, Sheffield and OPUS studies were not included because follow-up data for
756 any fracture were not available.

757 [c] The HUNT, Cardiovascular Health Study, Leiden 85-plus and PROSPER studies were not included because follow-up
758 data for non-spine fractures were not available.

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

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

762 All HRs were age and sex-adjusted. The multivariable analysis yielded similar results (eTable 3).

Figure 3. Association between subclinical hyperthyroidism and the risk of fracture by TSH category

Abbreviations: CI, confidence interval; HR, hazard ratio; TSH, thyroid-stimulating hormone

[a] The PROSPER study was not included because follow-up data were only available for any fracture

[b] The HUNT, Cardiovascular Health Study, Sheffield and OPUS 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 non-spine 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.

All HRs were age and sex-adjusted. The multivariable analysis yielded similar results (eTable 3).

Table 1. Baseline characteristics of individuals in included studies (n = 70,298)

Study	Description of Study Sample	No. of Participants	Age Median (Range), y [a]	Women	No. (%)		Thyroid Medication Users, No. (%) [c]		Follow-up [d]		
					Subclinical Hypothyroidism [b]	Subclinical Hyperthyroidism [b]	At Baseline	During Follow-Up	Start, y	Duration, Median (IQR), y	Person-Years
United States											
Cardiovascular Health Study[8]	CDAs with Medicare eligibility in 4 US communities	3555	71 (65-100)	2185 (61.5)	543 (15.3)	159 (4.5)	295 (8.3)	629 (17.7)	1989-1990	12.8 (7.5-18.8)	45,160
Health ABC Study[56]	CDAs aged 70-79y with Medicare eligibility in 2 US communities	2764	74 (69-81)	1407 (50.9)	335 (12.1)	82 (3.0)	267 (9.7)	383 (13.9)	1997	12.8 (8.1-13.2)	29,292
Osteoporotic Fractures in Men (MrOS)[7]	CDMs aged 65+ in 6 US clinical centers	1588	73 (65-99)	0 (0.0)	147 (9.3)	30 (1.9)	121 (7.6)	152 (9.6)	2000-2002	11.1 (8.0-11.8)	15,133
Europe											
EPIC-Norfolk Study[46]	Adults aged 45-79 y living in Norfolk, England	13,066	58 (40-78)	7104 (54.4)	720 (5.5)	360 (2.8)	439 (3.4)	NA	1995-1998	12.4 (11.6-13.3)	155,661
HUNT Study[57], [e]	Adults living in Nord-Trøndelag County, Norway	33,646	57 (19-99)	22,988 (68.3)	1313 (3.9)	945 (2.8)	1576 (4.7)	NA	1995-1997	12.2 (11.6-12.8)	369,413
Invecchiare in Chianti Study (InCHIANTI)[21]	CDAs aged 65y+ living in Tuscany, Italy	1186	71 (21-102)	664 (56.0)	33 (2.8)	87 (7.3)	28 (2.4)	48 (4.0)	1998	9.1 (7.2-9.3)	9393
Leiden 85-plus Study[58]	All adults aged 85y living in Leiden, the Netherlands	514	85 (85-85)	336 (65.4)	35 (6.8)	23 (4.5)	17 (3.3)	29 (5.6)	1997-1999	4.9 (2.2-8.2)	2736
Osteoporosis and Ultrasound Study (OPUS)[41], [f]	Women aged 20-80y living in Germany, France, UK	1433	63 (20-80)	1433 (100.0)	12 (0.8)	216 (15.1)	0 (0.0)	NA	1999-2001	6.0 (5.8-6.3)	8556
PROSPER Study[18]	Older community-dwelling adults at high cardiovascular risk in the Netherlands, Ireland and Scotland	5563	75 (69-83)	2824 (50.8)	306 (5.5)	133 (2.4)	184 (3.3)	252 (4.5)	1997-1999	3.2 (3.0-3.5)	17162
Rotterdam Study[59]	Adults aged 55y+ living in Rotterdam, the Netherlands	1838	69 (55-93)	1127 (61.3)	107 (5.8)	120 (6.5)	42 (2.3)	NA	1989-1992	15.2 (10.2-16.2)	24,031
Sheffield Study[6]	Women aged 50-85y living in Sheffield, UK	334	63 (50-86)	334 (100.0)	32 (9.6)	11 (3.3)	5 (1.5)	21 (6.3)	1990-1991	10.0 (5.3-10.1)	2597
Australia											
Busselton Health Study[19]	Adults living in Busselton, Western Australia	2049	51 (18-90)	1006 (49.1)	89 (4.3)	53 (2.6)	19 (0.9)	34 (1.7)	1981	20.0 (17.2-20.0)	35,607
Asia											
Nagasaki Adult Health Study[20]	Atomic bomb survivors in Nagasaki, Japan	2762	57 (38-92)	1686 (61.0)	420 (15.2)	NA [g]	39 (1.4)	6 (0.2)	1984-1987	20.2 (10.0-25.9)	47,660
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 (8.3-13.0)**	**762,401**

Abbreviations: CDA, community-dwelling adults; CDM, community-dwelling men; EPIC, European Prospective Investigation of Cancer; Health ABC Study, Health Aging and Body Composition Study; HUNT, Nord-Trøndelag Health Study; IQR, inter-quartile range (25th-75th percentiles); NA, not available; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; y, years

[a] Participants younger than 18 years old 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.

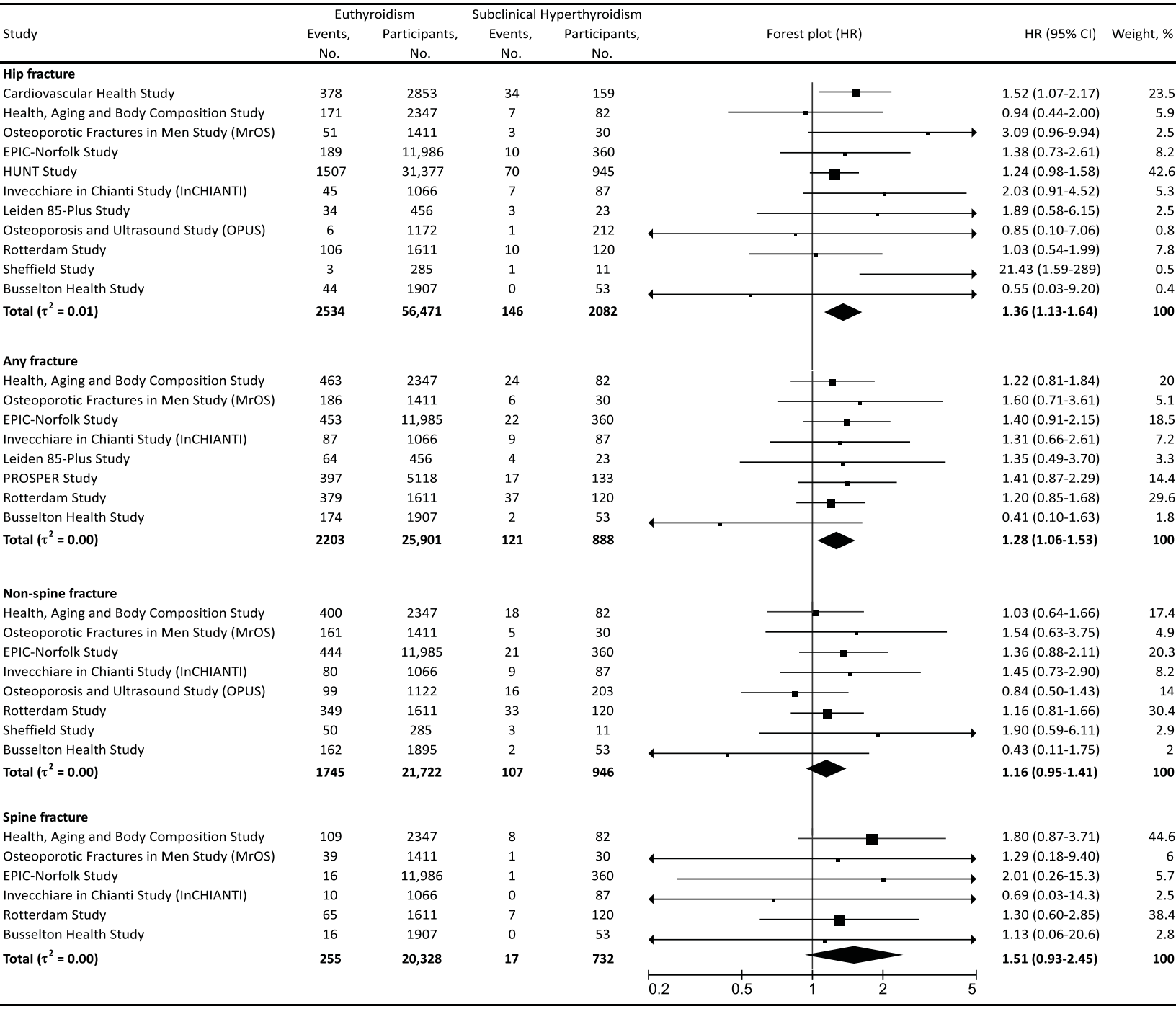
[c] Data on baseline thyroid medication use (thyroxine, antithyroid drugs) were unavailable for 273 participants of the HUNT study, 1 participant of the Cardiovascular Health Study, 64 participants of the Osteoporotic Fractures in Men (MrOS) study, 8 participants of the Health ABC study and 1 participant of the Rotterdam study. Data on thyroid medication use during follow-up were unavailable for 294 participants of the Osteoporotic Fractures in Men (MrOS) 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.

[d] 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.

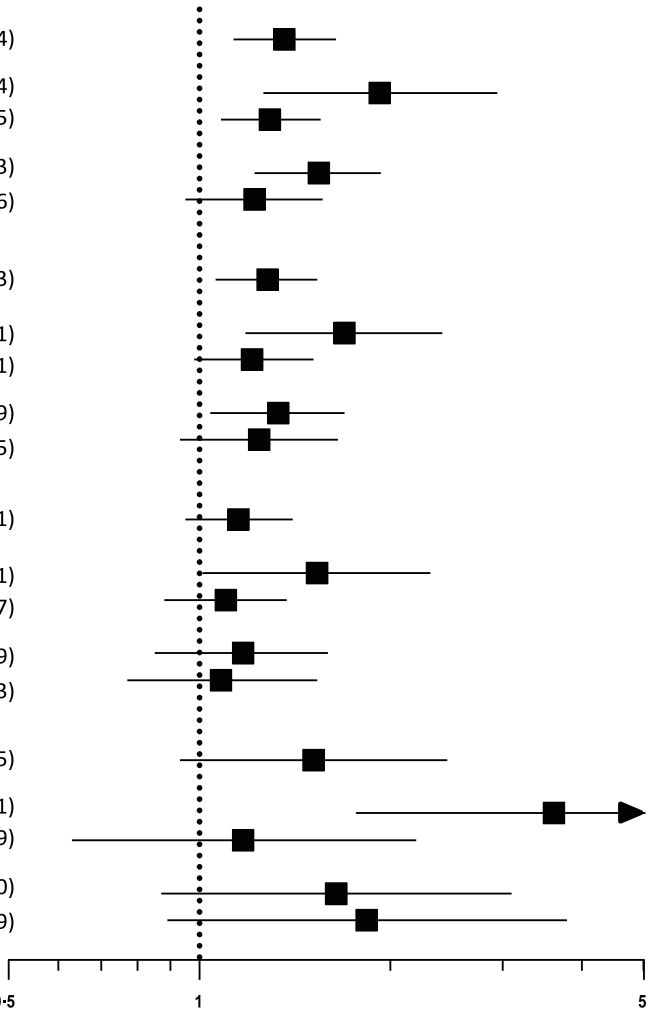
[e] The sample included for the original article of the HUNT study used several inclusion/exclusion criteria that differed from those used here (such as excluding participants younger than 40 years, those with previous fractures or previous thyroid disease), resulting in different numbers of participants.

[f] The original Osteoporosis and Ultrasound Study (OPUS) was a population-based study with no exclusions. The sample included here is the thyroid hormone sub-study of OPUS, which excluded thyroid medication users.

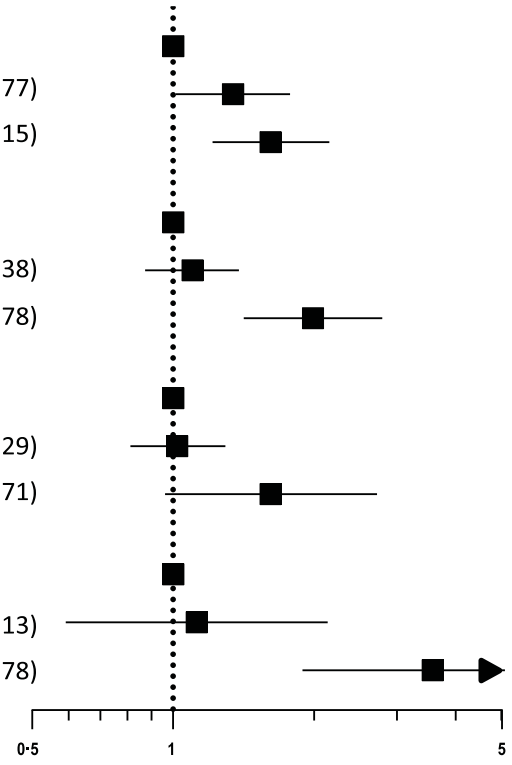
[g] 21 participants with TSH < 0.45mIU/L and free thyroxine within the normal range were excluded from the Nagasaki cohort due to the use of a first-generation TSH assay that is not sensitive enough to detect subclinical hyperthyroidism


Study
Euthyroidism
Events, No.
Participants, No.
Subclinical Hyperthyroidism
Events, No.
Participants, No.
Forest plot (HR)
HR (95% CI)
Weight, %
Hip fracture
Cardiovascular Health Study 378 2853 34 159 1.52 (1.07-2.17) 23.5
Health, Aging and Body Composition Study 171 2347 7 82 0.94 (0.44-2.00) 5.9
Osteoporotic Fractures in Men Study (MrOS) 51 1411 3 30 3.09 (0.96-9.94) 2.5
EPIC-Norfolk Study 189 11,986 10 360 1.38 (0.73-2.61) 8.2
HUNT Study 1507 31,377 70 945 1.24 (0.98-1.58) 42.6
Invecchiare in Chianti Study (InCHIANTI) 45 1066 7 87 2.03 (0.91-4.52) 5.3
Leiden 85-Plus Study 34 456 3 23 1.89 (0.58-6.15) 2.5
Osteoporosis and Ultrasound Study (OPUS) 6 1172 1 212 0.85 (0.10-7.06) 0.8
Rotterdam Study 106 1611 10 120 1.03 (0.54-1.99) 7.8
Sheffield Study 3 285 1 11 21.43 (1.59-289) 0.5
Busselton Health Study 44 1907 0 53 0.55 (0.03-9.20) 0.4
Total (τ^2 = 0.01) 2534 56,471 146 2082 1.36 (1.13-1.64) 100
Any fracture
Health, Aging and Body Composition Study 463 2347 24 82 1.22 (0.81-1.84) 20
Osteoporotic Fractures in Men Study (MrOS) 186 1411 6 30 1.60 (0.71-3.61) 5.1
EPIC-Norfolk Study 453 11,985 22 360 1.40 (0.91-2.15) 18.5
Invecchiare in Chianti Study (InCHIANTI) 87 1066 9 87 1.31 (0.66-2.61) 7.2
Leiden 85-Plus Study 64 456 4 23 1.35 (0.49-3.70) 3.3
PROSPER Study 397 5118 17 133 1.41 (0.87-2.29) 14.4
Rotterdam Study 379 1611 37 120 1.20 (0.85-1.68) 29.6
Busselton Health Study 174 1907 2 53 0.41 (0.10-1.63) 1.8
Total (τ^2 = 0.00) 2203 25,901 121 888 1.28 (1.06-1.53) 100
Non-spine fracture
Health, Aging and Body Composition Study 400 2347 18 82 1.03 (0.64-1.66) 17.4
Osteoporotic Fractures in Men Study (MrOS) 161 1411 5 30 1.54 (0.63-3.75) 4.9
EPIC-Norfolk Study 444 11,985 21 360 1.36 (0.88-2.11) 20.3
Invecchiare in Chianti Study (InCHIANTI) 80 1066 9 87 1.45 (0.73-2.90) 8.2
Osteoporosis and Ultrasound Study (OPUS) 99 1122 16 203 0.84 (0.50-1.43) 14
Rotterdam Study 349 1611 33 120 1.16 (0.81-1.66) 30.4
Sheffield Study 50 285 3 11 1.90 (0.59-6.11) 2.9
Busselton Health Study 162 1895 2 53 0.43 (0.11-1.75) 2
Total (τ^2 = 0.00) 1745 21,722 107 946 1.16 (0.95-1.41) 100
Spine fracture
Health, Aging and Body Composition Study 109 2347 8 82 1.80 (0.87-3.71) 44.6
Osteoporotic Fractures in Men Study (MrOS) 39 1411 1 30 1.29 (0.18-9.40) 6
EPIC-Norfolk Study 16 11,986 1 360 2.01 (0.26-15.3) 5.7
Invecchiare in Chianti Study (InCHIANTI) 10 1066 0 87 0.69 (0.03-14.3) 2.5
Rotterdam Study 65 1611 7 120 1.30 (0.60-2.85) 38.4
Busselton Health Study 16 1907 0 53 1.13 (0.06-20.6) 2.8
Total (τ^2 = 0.00) 255 20,328 17 732 1.51 (0.93-2.45) 100
0.2
0.5
1
2
5

		Euthyroidism		Subclinical Hyperthyroidism		HR (95% CI)	Forrest plot (HR)	P for interaction
		Events	Participants	Events	Participants			
Hip fracture [a]								
Overall		2534	56,471	146	2082	1.36 (1.13-1.64)		
Sex	Men	606	21,854	22	468	1.92 (1.26-2.94)		0.09
	Women	1928	34,617	124	1614	1.29 (1.08-1.55)		
Age [e]	< 75 years	1360	47,540	78	1646	1.54 (1.22-1.93)		0.18
	≥ 75 years	1162	8462	67	431	1.22 (0.95-1.56)		
Any fracture [b]								
Overall		2203	25,901	121	888	1.28 (1.06-1.53)		
Sex	Men	796	13,091	32	327	1.69 (1.18-2.41)		0.12
	Women	1407	12,810	89	561	1.21 (0.98-1.51)		
Age [e]	< 75 years	1363	20,067	69	649	1.33 (1.04-1.69)		0.72
	≥ 75 years	840	5834	52	239	1.24 (0.93-1.65)		
Non-spine fracture [c]								
Overall		1745	21,722	107	946	1.16 (0.95-1.41)		
Sex	Men	592	10,326	24	282	1.53 (1.01-2.31)		0.17
	Women	1153	11,396	83	664	1.10 (0.88-1.37)		
Age [e]	< 75 years	1218	18,707	69	766	1.17 (0.85-1.59)		0.74
	≥ 75 years	527	2847	36	175	1.08 (0.77-1.53)		
Spine fracture [d]								
Overall		255	20,328	17	732	1.51 (0.93-2.45)		
Sex	Men	106	10,332	7	282	3.61 (1.76-7.41)		0.02
	Women	149	9996	10	450	1.17 (0.63-2.19)		
Age [e]	< 75 years	167	17,476	9	581	1.64 (0.87-3.10)		0.82
	≥ 75 years	86	2732	8	148	1.83 (0.89-3.79)		



	Euthyroidism		Subclinical Hyperthyroidism		HR (95% CI)	Forrest plot (HR)	P for trend
	Events	Participants	Events	Participants			
Hip fracture[a]							
TSH 0.45-4.49 mIU/L	2534	56,471			1 (ref)		
0.10-0.44 mIU/L			99	1568	1.34 (1.01-1.77)		0.001
< 0.10 mIU/L			47	510	1.61 (1.21-2.15)		
Any fracture[b]							
TSH 0.45-4.49 mIU/L	2203	25,901			1 (ref)		
0.10-0.44 mIU/L			77	676	1.10 (0.87-1.38)		< 0.001
< 0.10 mIU/L			44	212	1.98 (1.41-2.78)		
Non-spine fracture[c]							
TSH 0.45-4.49 mIU/L	1745	21,722			1 (ref)		
0.10-0.44 mIU/L			74	757	1.02 (0.81-1.29)		0.07
< 0.10 mIU/L			32	185	1.61 (0.96-2.71)		
Spine fracture[d]							
TSH 0.45-4.49 mIU/L	255	20,328			1 (ref)		
0.10-0.44 mIU/L			9	566	1.12 (0.59-2.13)		< 0.001
< 0.10 mIU/L			8	162	3.57 (1.88-6.78)		



Supplementary Online Material

eMethods: Study Quality Assessment

eTable 1: Definitions of Subclinical Thyroid Dysfunction and Fracture Events

eTable 2: Quality Assessment of Included Studies [a]

eTable 3: Stratified analyses for the association between subclinical hyperthyroidism and the risk of fractures

eTable 4: Sensitivity analyses on the association between subclinical hyperthyroidism and the risk of fractures

eTable 5: Persistent thyroid function state and fracture risk

eTable 6: Analysis stratified by publication status of fracture data

eTable 7: Stratified analyses for the association between subclinical hypothyroidism and the risk of fractures

eTable 8: Sensitivity analyses on the association between subclinical hypothyroidism and the risk of fractures

eTable 9: Analysis on the association of thyroid medication treatment and fracture risk (treated vs. untreated)

eFigure 1: Flow Chart of Studies Evaluated for Inclusion in the Individual Participant Data

eFigure 2: Forest plots of the association between subclinical hypothyroidism and the risk of fractures

References

eMethods: Study Quality Assessment

The Newcastle-Ottawa Quality Assessment Scale[1] items assessed were: 1-2) representativeness of the exposed/unexposed cohort (population-based vs. convenience-based), 3) ascertainment of exposure (thyroid function measurement), 4) availability of relevant confounders for adjustment, 5) assessment of outcome with objective fracture assessment (defined as using radiographic images and/or reviewing radiologists or orthopedic reports and other support documents to verify clinical diagnoses; or record linkage on database records) and formal adjudication procedure (defined as using predefined criteria applied by experts), 6) length of follow-up period, and 7) loss to follow-up. We did not list the presence of outcome (current fracture) at cohort study start, as we excluded participants with acute fracture at baseline from the analysis. Study quality was assessed independently by two authors (M.R.B and T.H.C.).

eTable 1: Definitions of Subclinical Thyroid Dysfunction and Fracture Events

Study	Subclinical hypothyroidism	Subclinical hyperthyroidism	Event definition[g]			
			Hip fracture	Any fracture	Non-spine fracture	Spine fracture
Busselton Health Study[2]	TSH ≥ 4.5mIU/L & TSH < 20mIU/L normal fT4 0.7-1.8ng/dL (9-23pmol/L) or missing fT4 (1/89, 1.1%)	TSH < 0.45mIU/L & normal fT4 0.7-1.8ng/dL (9-23pmol/L) or missing fT4 (1/53, 1.9%). fT3 value not available for SA	ICD10: S72.0-1	Non-spine or spine fracture (first event)	Including: ICD9: 807-829 Excluding: skull/face (ICD9: 800-804)	Cervical (ICD10: S12), thoracic (ICD10: S22), lumbar (ICD10: S32) vertebrae, vertebral fracture of unknown location (ICD10: T08); clinically diagnosed
Cardiovascular Health Study[3]	TSH ≥ 4.5mIU/L & TSH < 20mIU/L normal fT4 0.7-1.7ng/dL (9-22pmol/L) or missing fT4 (0/543, 4.2%)	TSH < 0.45mIU/L & normal fT4 0.7-1.7ng/dL (9-22pmol/L) or missing fT4 (96/159, 60.4%) [b]. fT3 value not available for SA	ICD9: 820.0-820.9 for inpatients, plus CPT procedure code on fracture treatment for outpatients [d]	NA	NA	NA
EPIC-Norfolk Study[4]	TSH ≥ 4.5mIU/L & TSH < 20mIU/L normal fT4 0.7-1.6ng/dL (9-20pmol/L) or missing fT4 (0/720, 0%)	TSH < 0.45mIU/L & normal fT4 0.7-1.6ng/dL (9-20pmol/L) or missing fT4 (0/360, 0%). fT3 value not available for SA	ICD10: S72.0-2	Non-spine or spine fracture (first event)	Excluding skull/face, ankle, fingers, toes	Thoracic (ICD10: S22) or lumbar (ICD10: S32) vertebrae, vertebral fracture of unknown location (ICD10: T08); clinically diagnosed
Health, ABC Study[5]	TSH ≥ 4.5mIU/L & TSH < 20mIU/L normal fT4 0.8-1.8ng/dL (10-23pmol/L) or missing fT4 (230/335, 68.7%) [c]	TSH < 0.45mIU/L & normal fT4 0.8-1.8ng/dL (10-23pmol/L) or missing fT4 (57/82, 69.5%). fT3 value not available for SA [c]	Femoral neck, intertrochanteric, proximal femur	Non-spine or spine fracture (first event)	Excluding ankle, fingers, toes	Thoracic or lumbar vertebrae; clinically diagnosed
HUNT Study[6]	TSH ≥ 4.5mIU/L & TSH < 20mIU/L normal fT4 0.6-1.6ng/dL (8-20pmol/L) or missing fT4 (0/814, 0%)	TSH < 0.45mIU/L & normal fT4 0.6-1.6ng/dL (8-20pmol/L) or missing fT4 (556/945, 58.8%) [a], & normal total T3 1.2-2.7nmol/L (only in SA)	ICD9: 824, SIFF-96 procedure codes [e]; ICD10: S72.0-2, S72.9, NCSP codes [f]	NA	NA	NA
Invecchiare in Chianti Study (InCHIANTI)[7]	TSH ≥ 4.5mIU/L & TSH < 20mIU/L normal fT4 0.8-2.2ng/dL (10-27pmol/L) or missing fT4 (0/33, 0%)	TSH < 0.45mIU/L & normal fT4 0.8-2.2ng/dL (10-27pmol/L) or missing fT4 (0/86, 0%), & normal fT3 4.3-8.1pmol/L (only in SA)	ICD9: 820	Non-spine or spine fracture (first event)	Excluding skull/face, ankle, fingers, toes	Thoracic (ICD9: 805.2-5) or lumbar (ICD9: 806.2-5) vertebrae; clinically diagnosed
Leiden 85-plus Study[8]	TSH ≥ 4.5mIU/L & TSH < 20mIU/L normal fT4 1.0-1.8ng/dL (13-23pmol/L) or missing fT4 (1/35, 2.9%)	TSH < 0.45mIU/L & normal fT4 1.0-1.8ng/dL (13-23pmol/L) or missing fT4 (0/23, 0%), & normal fT3 4.7-8.2pmol/L (only in SA)	Any hip fracture	Any fracture	NA	NA
Osteoporotic Fractures in Men (MrOS) Study[9]	TSH ≥ 4.5mIU/L & TSH < 20mIU/L normal fT4 0.7-1.85ng/dL (9-24pmol/L) or missing fT4 (0/147, 0%)	TSH < 0.45mIU/L & normal fT4 0.7-1.85ng/dL (9-24pmol/L) or missing fT4 (0/30, 0%). fT3 value not available for SA	Femoral neck, intertrochanteric, subtrochanteric fracture	Non-spine or spine fracture (first event)	Excluding skull/face, ankle, fingers, toes	Thoracic or lumbar vertebrae; clinically diagnosed
Nagasaki Adult Health Study[10]	TSH ≥ 4.5mIU/L & TSH < 20mIU/L normal fT4 0.8-2.5ng/dL (10-32pmol/L) or missing fT4 (0/420, 0%)	TSH < 0.45mIU/L & normal fT4 0.8-2.5ng/dL (10-32pmol/L) or missing fT4 (0/0, 0%). fT3 value not available for SA	Any hip fracture	NA	NA	NA
Osteoporosis and Ultrasound Study (OPUS)[11]	TSH ≥ 4.5mIU/L & TSH < 20mIU/L normal fT4 0.7-1.8ng/dL (9-23pmol/L) or missing fT4 (0/12, 0%)	TSH < 0.45mIU/L & normal fT4 0.7-1.8ng/dL (9-23pmol/L) or missing fT4 (1/204, 0.5%), & normal fT3 2.5-5.7pmol/L (only in SA)	Any low-traumatic hip fracture	NA	Any low-traumatic non-spine fracture	NA
PROSPER Study[12]	TSH ≥ 4.5mIU/L & TSH < 20mIU/L normal fT4 0.9-1.4ng/dL (12-18pmol/L) or missing fT4 (12/306, 3.9%)	TSH < 0.45mIU/L & normal fT4 0.9-1.4ng/dL (12-18pmol/L) or missing fT4 (7/133, 5.3%). fT3 value not available for SA	NA	Any fracture	NA	NA
Rotterdam Study[13]	TSH ≥ 4.5mIU/L & TSH < 20mIU/L normal fT4 0.9-1.9ng/dL (11-25pmol/L) or missing fT4 (35/107, 32.7%)	TSH < 0.45mIU/L & normal fT4 0.9-1.9ng/dL (11-25pmol/L) or missing fT4 (27/120, 22.5%). fT3 value not available for SA	Any hip fracture	Non-spine or spine fracture (first event)	Excluding skull, ankle/foot, fingers/hand/wrist	Any vertebral fracture; clinically diagnosed
Sheffield Study[14]	TSH ≥ 4.5mIU/L & TSH < 20mIU/L normal fT4 0.9-1.7ng/dL (12-22pmol/L) or missing fT4 (0/32, 0%)	TSH < 0.45mIU/L & normal fT4 0.9-1.7ng/dL (12-22pmol/L) or missing fT4 (0/11, 0%). fT3 value not available for SA	Any hip fracture	NA	Any non-spine fracture	NA

Abbreviations: CPT, current procedural terminology; fT3, free triiodothyronine; fT4, free thyroxine; NA, not available; TSH, thyroid-stimulating hormone; y, years.
[a] fT4 was measured only in participants with TSH < 0.20mIU/L
[b] fT4 was measured only in participants with TSH ≤ 0.10mIU/L
[c] fT4 was measured only in participants with TSH ≤ 0.10mIU/L or TSH ≥ 7.00mIU/L
[d] CPT procedure codes 27125-27127, 27130-27131, 27230-27248, 29010-29046, 29305-29365, 29505-29520, 29799.
[e] Third Norwegian national classification of surgical procedures (SIFF-96) codes 8072, 8073, 8079, 8103, 8106, 8332, 8334, 8336 and 8339
[f] Nomesco Classification of Surgical Procedures (NCS) codes NFB 00-03, 09-13, 19-20, 30, 40, 59, 99, NFJ 00-03, 10-13, 20-23, 30-33, 40-43, 50-55, 60-63, 70-73, 80-83, 90-93, TNF40
[g] For spine fractures, cervical and sacral fractures were excluded when data allowed, as these fractures usually occur in high-energy trauma. For other fracture outcomes, data on trauma mechanism were generally unavailable.

eTable 2: Quality Assessment of Included Studies [a]

Study	Design	Setting	Ascertainment of exposure [b]	Controlling for the most important factors [c]	Controlling for any additional factors [c]	Methods for fracture assessment	Formal adjudication of fractures [d]	Adjudication blinded to thyroid status	Loss to follow-up	Duration of follow-up, median (IQR)
Busselton Health Study	Prospective cohort study	Population-based	Third generation TSH assay	Age, gender, BMI, smoking status	History of diabetes, thyroid medication, anti-osteoporotic medication	Hospital discharge records: diagnoses coded with ICD9 and ICD10	no	NA	5%	20.0 (17.2-20.0)
Cardiovascular Health Study	Prospective cohort study	Population-based	Third generation TSH assay	Age, gender, BMI, smoking status	History of diabetes, thyroid and thyroid-altering medication, anti-osteoporotic medication	Interview and hospital records reviewed by experts	no	NA	0%	12.8 (7.5-18.8)
EPIC-Norfolk Study	Prospective cohort study	Population-based	Third generation TSH assay	Age, gender, BMI, smoking status	History of diabetes, thyroid and thyroid-altering medication	Hospital discharge coding by data linkage with NHS central register	yes	yes	1.3%	12.4 (11.6-13.3)
Health ABC Study	Prospective cohort study	Population-based	Third generation TSH assay	Age, gender, BMI, smoking status	History of diabetes, thyroid and thyroid-altering medication, anti-osteoporotic medication	Interview, hospital records, and other support documents reviewed by a panel of clinicians	yes	yes	<5%	12.8 (8.1-13.2)
HUNT Study	Prospective cohort study	Population-based	Third generation TSH assay	Age, gender, BMI, smoking status	History of diabetes, thyroid or thyroid-altering medication	Hospital records and radiology reports reviewed by physicians, health secretaries and nurses	yes	yes	<5%	12.2 (11.6-12.8)
Invecchiare in Chianti (InCHIANTI) Study	Prospective cohort study	Population-based	Third generation TSH assay	Age, gender, BMI, smoking status	History of diabetes, thyroid and thyroid-altering medication, anti-osteoporotic medication	Hospital records and other support documents	yes	yes	<5%	9.1 (7.2-9.3)
Leiden 85-plus Study	Prospective cohort study	Population-based	Third generation TSH assay	Age, gender, BMI, smoking status	History of diabetes, thyroid and thyroid-altering medication, anti-osteoporotic medication	Annual interview of treating general practitioner or nursing home physician and review of all medical records of general practitioners / nursing home physicians	no	NA	<4%	4.9 (2.2-8.2)
Osteoporotic Fractures in Men (MrOS) Study	Random sample of a prospective cohort study	Population-based	Third generation TSH assay	Age, gender, BMI, smoking status	History of diabetes, thyroid and thyroid-altering medication, anti-osteoporotic medication	Interview-reported fractures centrally adjudicated by physician through radiology reports or X-rays	yes	yes	2%	11.1 (8.0-11.8)
Nagasaki Adult Health Study	Prospective cohort study	Population-based	First generation TSH assay [e]	Age, gender, BMI, smoking status	History of diabetes, thyroid medication	Interview of participants	no	NA	7.3%	20.2 (10.0-25.9)
Osteoporosis and Ultrasound Study (OPUS)	Prospective cohort study	Population-based	Third generation TSH assay	Age, gender, BMI, smoking status	Thyroid and thyroid-altering medication, anti-osteoporotic medication	Interview after 6y follow-up, validated through medical records and imaging reviewed by a radiologist	yes	yes	40%	6.0 (5.8-6.3)
PROSPER Study	Prospective cohort study [f]	Population-based	Third generation TSH assay	Age, gender, BMI, smoking status	History of diabetes, thyroid and thyroid-altering medication	Fractures documented as adverse events	no	NA	<1%	3.2 (3.0-3.5)
Rotterdam Study	Prospective cohort study	Population-based	Third generation TSH assay	Age, gender, BMI, smoking status	History of diabetes, thyroid medication	General practitioner and hospital registry records, reviewed by independent medical experts in the field	yes	yes	<1%	15.2 (10.2-16.2)
Sheffield Study	Prospective cohort study	Population-based	Third generation TSH assay	Age, gender, BMI, smoking status	History of diabetes, thyroid medication	General practitioner records, and interview, if confirmed by radiology or orthopedic report	yes	yes	2%	10.0 (5.3-10.1)

Abbreviations: BMI, body mass index; IQR, interquartile range; NA, not applicable; TSH, thyroid-stimulating hormone

[a] Based on the individual items of the Newcastle-Ottawa Quality Assessment Scale[1]. Absence of the outcome at baseline was not included in this list as participants with acute fracture at baseline were excluded from the analysis.

[b] Third generation TSH assays have a functional sensitivity of 0.01-0.02mIU/l (the lowest TSH level at which interassay coefficient of variation is <20%), making this a highly precise measurement.

[c] By design the individual participant data analysis allowed the adjustment of multiple factors done in a stepwise manner: primary analyses and the multivariable model (left column), followed by sensitivity analyses (right column).

[d] Formal adjudication was defined as formal report by each cohort on application of predefined criteria by experts to each fracture event.

[e] The Nagasaki Adult Health Study used a first generation TSH assay and was excluded from the analysis on subclinical hyperthyroidism.

[f] Based on both arms of a randomized controlled trial of Pravastatin vs. Placebo, without any intervention on thyroid function.

eTable 3: Stratified analyses for the association between subclinical hyperthyroidism and the risk of fractures

	Hip fracture [a]						Any fracture [b]					
	Euthyroidism		Subclinical Hyperthyroidism		HR (95% CI)		Euthyroidism		Subclinical Hyperthyroidism		HR (95% CI)	
	Events	Participants	Events	Participants	Age/Sex-adjusted	Multivariable Model [e]	Events	Participants	Events	Participants	Age/Sex-adjusted	Multivariable Model [e]
Total population	2534	56,471	146	2082	1.36 (1.13-1.64)	1.37 (1.11-1.70)	2203	25,901	121	888	1.28 (1.06-1.53)	1.27 (1.06-1.53)
Sex												
Men	606	21,854	22	468	1.92 (1.26-2.94)	1.96 (1.28-3.00)	796	13,091	32	327	1.69 (1.18-2.41)	1.73 (1.21-2.47)
Women	1928	34,617	124	1614	1.29 (1.08-1.55)	1.28 (1.04-1.58)	1407	12,810	89	561	1.21 (0.98-1.51)	1.21 (0.97-1.50)
P for interaction					0.09	0.08					0.12	0.10
Age [f]												
< 75 years	1360	47,540	78	1646	1.54 (1.22-1.93)	1.59 (1.19-2.12)	1363	20,067	69	649	1.33 (1.04-1.69)	1.32 (1.04-1.69)
≥ 75 years	1162	8462	67	431	1.22 (0.95-1.56)	1.21 (0.93-1.56	840	5834	52	239	1.24 (0.93-1.65)	1.22 (0.92-1.63)
P for interaction					0.18	0.17					0.72	0.68
TSH												
0.45-4.49 mIU/L	2534	56,471			1 (ref)	1 (ref)	2203	25,901			1 (ref)	1 (ref)
0.10-0.44 mIU/L			99	1568	1.34 (1.01-1.77)	1.33 (1.01-1.76)			77	676	1.10 (0.87-1.38)	1.10 (0.87-1.38)
< 0.10 mIU/L			47	510	1.61 (1.21-2.15)	1.57 (1.17-2.10)			44	212	1.98 (1.41-2.78)	1.92 (1.37-2.69)
P for trend					0.001	0.003					< 0.001	< 0.001
	Non-spine fracture [c]						**Spine fracture [d]**					
Total population	1745	21,722	107	946	1.16 (0.95-1.41)	1.16 (0.95-1.41)	255	20,328	17	732	1.51 (0.93-2.45)	1.49 (0.92-2.42)
Sex												
Men	592	10,326	24	282	1.53 (1.01-2.31)	1.56 (1.03-2.37)	106	10,332	7	282	3.61 (1.76-7.41)	3.78 (1.83-7.80)
Women	1153	11,396	83	664	1.10 (0.88-1.37)	1.10 (0.88-1.38)	149	9996	10	450	1.17 (0.63-2.19)	1.16 (0.62-2.16)
P for interaction					0.17	0.15					0.02	0.02
Age [f]												
< 75 years	1218	18,707	69	766	1.17 (0.85-1.59)	1.18 (0.87-1.61)	167	17,476	9	581	1.64 (0.87-3.10)	1.58 (0.83-2.97)
≥ 75 years	527	2847	36	175	1.08 (0.77-1.53)	1.07 (0.75-1.52)	86	2732	8	148	1.83 (0.89-3.79)	1.88 (0.91-3.89)
P for interaction					0.74	0.68					0.82	0.73
TSH												
0.45-4.49 mIU/L	1745	21,722			1 (ref)	1 (ref)	255	20,328			1 (ref)	1 (ref)
0.10-0.44 mIU/L			74	757	1.02 (0.81-1.29)	1.03 (0.81-1.30)			9	566	1.12 (0.59-2.13)	1.15 (0.61-2.17)
< 0.10 mIU/L			32	185	1.61 (0.96-2.71)	1.59 (0.94-2.70)			8	162	3.57 (1.88-6.78)	3.31 (1.71-6.41)
P for trend					0.07	0.08					< 0.001	< 0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; TSH, thyroid-stimulating hormone

[a] The PROSPER study was not included because follow-up data were only available for any fracture

[b] The HUNT, Cardiovascular Health Study, Sheffield and OPUS 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 non-spine 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.

[e] Adjusted for age, sex, body mass index and smoking status. Complete case analysis was used, as missing data rate was <3% and unlikely to introduce relevant bias into the multivariable models[15,16].

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

eTable 4: Sensitivity analyses on the association between subclinical hyperthyroidism and the risk of fractures

	Hip fracture					Any fracture				
	Euthyroidism		Subclinical Hyperthyroidism		HR (95% CI)	Euthyroidism		Subclinical Hyperthyroidism		HR (95% CI)
	Events	Participants	Events	Participants		Events	Participants	Events	Participants	
All eligible studies										
Random-effects model	2534	56,471	146	2082	1.36 (1.13-1.64)	2203	25,901	121	888	1.28 (1.06-1.53)
Fixed-effects model	2534	56,471	146	2082	1.35 (1.14-1.60)	2203	25,901	121	888	1.28 (1.07-1.54)
Definition of Subclinical Hyperthyroidism										
Excluding those with missing FT4	2534	56,471	77	1344	1.39 (1.10-1.76)	2203	25,901	94	796	1.31 (1.07-1.62)
Excluding those with abnormal free or total T3	2500	56,015	143	2021	1.38 (1.11-1.71)	2139	25,445	117	857	1.28 (1.06-1.55)
Applying age-specific TSH reference ranges [a]	2373	55,166	196	2438	1.32 (1.14-1.53)	2044	24,813	151	1104	1.23 (1.04-1.45)
Medication use										
Excluding users of thyroid medication at baseline [b]	2414	54,737	87	1430	1.52 (1.19-1.93)	2113	25,177	99	710	1.42 (1.16-1.74)
Excluding users of thyroid medication at baseline or during follow-up [b]	2381	54,464	83	1399	1.54 (1.19-1.99)	2092	25,043	94	684	1.42 (1.15-1.75)
Excluding users of thyroid and thyroid-altering medication [b]	2341	53,378	83	1385	1.47 (1.18-1.83)	2048	24,649	95	689	1.39 (1.13-1.71)
Excluding users of anti-osteoporotic medication at baseline [c]	2516	56,303	144	2063	1.39 (1.12-1.72)	2162	25,759	115	873	1.27 (1.05-1.54)
Outcomes										
Only studies with formal adjudication procedures [d]	2078	51,255	109	1847	1.36 (1.01-1.81)	1568	18,420	98	686	1.29 (1.05-1.58)
Only studies with most uniform definition of fracture	2534	56,471	146	2082	1.36 (1.13-1.64)	1650	22,383	82	715	1.35 (1.08-1.69)
Excluded Studies										
Excluding study inconsistent with proportional hazard assumption [e]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Excluding small study because of potential publication bias [f]	2531	56,186	145	2071	1.33 (1.13-1.58)	NA	NA	NA	NA	NA
Excluding study with >5% loss to follow-up [g]	2528	55,299	145	1870	1.38 (1.12-1.70)	NA	NA	NA	NA	NA
Excluding study with less objective outcome ascertainment [h]	NA	NA	NA	NA	NA	1824	20,783	104	755	1.26 (1.03-1.53)
Further adjustments of multivariable models										
Plus history of diabetes mellitus at baseline	2395	53,731	137	1793	1.38 (1.09-1.75)	2 163	25,442	120	859	1.27 (1.05-1.53)
	Non-spine fracture					**Spine fracture**				
All eligible studies										
Random-effects model	1745	21,722	107	946	1.16 (0.95-1.41)	255	20,328	17	732	1.51 (0.93-2.45)
Fixed-effects model	1745	21,722	107	946	1.16 (0.95-1.41)	255	20,328	17	732	1.51 (0.93-2.45)
Definition of Subclinical Hyperthyroidism										
Excluding those with missing FT4	1745	21,722	86	860	1.18 (0.95-1.47)	255	20,328	11	647	1.90 (0.98-3.68)
Excluding those with abnormal free or total T3	1745	21,722	106	910	1.17 (0.96-1.43)	255	20,328	17	724	1.51 (0.93-2.46)
Applying age-specific TSH reference ranges [a]	1638	21,078	132	1099	1.13 (0.94-1.35)	235	19,724	21	856	1.48 (0.95-2.30)
Medication use										
Excluding users of thyroid medication at baseline [b]	1675	21,137	89	779	1.26 (1.00-1.61)	240	19,745	13	567	1.74 (1.01-2.99)
Excluding users of thyroid medication at baseline or during follow-up [b]	1660	21,030	86	764	1.24 (1.00-1.55)	236	19,645	12	553	1.65 (0.94-2.91)
Excluding users of thyroid and thyroid-altering medication [b]	1617	20,634	85	758	1.23 (0.98-1.53)	232	19,242	13	546	1.79 (1.04-3.09)
Excluding users of anti-osteoporotic medication at baseline [c]	1703	21,567	103	927	1.17 (0.96-1.44)	246	20,191	15	717	1.45 (0.87-2.42)
Outcomes										
Only studies with formal adjudication procedures [d]	1583	19,827	105	893	1.18 (0.96-1.44)	239	18,421	17	679	1.52 (0.93-2.49)
Only studies with most uniform definition of fracture	1596	20,315	88	732	1.19 (0.96-1.48)	174	16,810	10	559	1.65 (0.89-3.07)
Excluded Studies										
Excluding study inconsistent with proportional hazard assumption [e]	1646	20,600	91	743	1.21 (0.98-1.50)	NA	NA	NA	NA	NA
Excluding small study because of potential publication bias [f]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Excluding study with >5% loss to follow-up [g]	1646	20,600	91	743	1.21 (0.98-1.50)	NA	NA	NA	NA	NA
Excluding study with less objective outcome ascertainment [h]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Further adjustments of multivariable models										
Plus history of diabetes mellitus at baseline	1610	20,163	90	715	1.20 (0.97-1.49)	252	19,889	17	704	1.51 (0.93-2.45)

Abbreviations: CI, confidence interval; FT4, free thyroxine; HR, hazard ratio (all age and sex adjusted, except for the last row); NA, data not applicable (no cohorts concerned by this sensitivity analysis); T3, triiodothyronine

[a] The TSH reference range for euthyroidism changed according to age group, as previously published[17]: TSH reference range was 0.45-4.49mIU/L for participants <75 years, 0.71-2.67mIU/L for 75-79.9 years, 0.60-6.16mIU/L for 80-84.9 years, 0.51-6.41mIU/L for 85-89.9 years, and 0.20-7.96mIU/L for participants aged 90 years or older.

[b] Thyroid medication includes thyroxine and anti-thyroid drugs; thyroid-altering medication includes oral corticosteroids, amiodarone and iodine.

[c] Anti-osteoporotic medication includes bisphosphonates, calcitonin, selective estrogen receptor modulator, parathyroid hormone.

[d] Formal adjudication procedures were defined as having clear criteria for the outcomes that were reviewed by experts for each potential case, which was performed in 8 studies.

[e] Excluding the Osteoporosis and Ultrasound study for non-spine fracture outcome (p=0.02).

[f] Excluding the Sheffield study for hip fracture outcome, which might be an outlier with no corresponding study of similar size with reduced fracture risk associated with subclinical hyperthyroidism (p=0.30).
[g] Excluding the Osteoporosis and Ultrasound study.
[h] Excluding the PROSPER study, which did not ascertain fractures with independent blind assessment or record linkage.

eTable 5: Persistent thyroid function state and fracture risk

A. Availability of repeated thyroid function testing data and persistent thyroid function state

Study	Participants			Interval to follow-up thyroid function test
	Baseline thyroid function test	Follow-up thyroid function test	Persistent thyroid function state [a]	
Cardiovascular Health Study	3555	2382	2073	4 years
HUNT Study	33,646	18,582	17,145	12 years
Leiden 85-plus Study	514	383	353	2 years
PROSPER Study	5563	5181	4836	6 months
Busselton Health Study	2049	1187	1090	13 years

B. Association between persistent subclinical thyroid dysfunction and risk of fractures

	Persistent euthyroidism		Persistent subclinical thyroid dysfunction		HR (95% CI)
	Events	Participants	Events	Participants	
Persistent subclinical hyperthyroidism					
Hip fracture	562	20,069	12	251	1.25 (0.58-2.65)
Any fracture	465	5943	12	93	1.48 (0.84-2.61)
Persistent subclinical hypothyroidism					
Hip fracture	562	20,069	32	341	1.36 (0.55-3.33)
Any fracture	465	5943	21	238	1.06 (0.68-1.63)

Abbreviations: CI, confidence interval; HR, hazard ratio

[a] Persistent thyroid function state is defined as persistent category (subclinical hypothyroidism, euthyroidism, subclinical hyperthyroidism) from baseline to follow-up thyroid function test

eTable 6: Analysis stratified by publication status of fracture data

A. Subclinical Hyperthyroidism

	Hip fracture						Any fracture					
	Euthyroidism		Subclinical Hyperthyroidism		HR (95% CI)	P for interaction	Euthyroidism		Subclinical Hyperthyroidism		HR (95% CI)	P for interaction
	Events	Participants	Events	Participants			Events	Participants	Events	Participants		
All studies	2534	56,471	146	2082	1.36 (1.13-1.64)		2203	25,901	121	888	1.28 (1.06-1.53)	
Excluding unpublished studies	2445	53,498	139	1942	1.35 (1.09-1.67)	0.45	1545	17,810	93	615	1.28 (1.04-1.58)	0.81
Excluding published studies	89	2973	7	140	1.84 (0.85-3.98)		658	8091	28	273	1.20 (0.73-1.95)	
	Non-spine fracture						Spine fracture					
All studies	1745	21,722	107	946	1.16 (0.95-1.41)		255	20,328	17	732	1.51 (0.93-2.45)	
Excluding unpublished studies	1503	18,761	96	806	1.15 (0.94-1.42)	0.72	229	17,355	17	592	1.56 (0.94-2.56)	0.69
Excluding published studies	242	2961	11	140	0.93 (0.30-2.92)		23	2973	0	140	0.89 (0.11-7.26)	

B. Subclinical Hypothyroidism

	Hip fracture						Any fracture					
	Euthyroidism		Subclinical Hypothyroidism		HR (95% CI)	P for interaction	Euthyroidism		Subclinical Hypothyroidism		HR (95% CI)	P for interaction
	Events	Participants	Events	Participants			Events	Participants	Events	Participants		
All studies	2600	58,637	229	3759	0.96 (0.83-1.10)		2203	25,901	204	1772	1.02 (0.89-1.18)	
Excluding unpublished studies	2445	53,498	213	3243	0.95 (0.83-1.10)	0.82	1545	17,810	153	1344	0.96 (0.81-1.14)	0.15
Excluding published studies	155	5139	16	516	1.05 (0.45-2.43)		658	8091	51	428	1.23 (0.92-1.64)	
	Non-spine fracture						Spine fracture					
All studies	1745	21,722	166	1473	1.06 (0.90-1.24)		255	20,328	24	1431	0.96 (0.59-1.55)	
Excluding unpublished studies	1503	18,761	147	1352	1.04 (0.86-1.25)	0.34	229	17,355	22	1309	0.92 (0.52-1.63)	0.47
Excluding published studies	242	2961	18	121	1.34 (0.83-2.14)		23	2973	2	122	1.64 (0.38-7.02)	

Abbreviations: CI, confidence interval; HR, hazard ratio

The following studies have not previously published their fracture data: Busselton Health Study, Invecchiare in Chianti (InCHIANTI) Study, Nagasaki Adult Health Study, PROSPER Study.

P for interaction values are calculated for comparing HR and 95% CI between published studies vs. unpublished studies.

eTable 7: Stratified analyses for the association between subclinical hypothyroidism and the risk of fractures

	Hip fracture [a]						Any fracture [b]					
	Euthyroidism		Subclinical Hypothyroidism		HR (95% CI)		Euthyroidism		Subclinical Hypothyroidism		HR (95% CI)	
	Events	Participants	Events	Participants	Age/Sex-adjusted	Multivariable Model [e]	Events	Participants	Events	Participants	Age/Sex-adjusted	Multivariable Model [e]
Total population	2600	58,637	229	3759	0.96 (0.83-1.10)	0.98 (0.85-1.14)	2203	25,901	204	1772	1.02 (0.89-1.18)	1.05 (0.90-1.24)
Sex												
Men	617	22,691	50	1202	0.99 (0.74-1.33)	1.07 (0.80-1.43)	796	13,091	53	681	0.90 (0.68-1.20)	0.92 (0.69-1.22)
Women	1983	35,946	179	2557	0.98 (0.82-1.16)	1.00 (0.81-1.23)	1407	12,810	151	1091	1.09 (0.92-1.29)	1.12 (0.92-1.36)
P for interaction					0.95	0.71					0.25	0.27
Age [f]												
< 75 years	1418	49,854	114	2856	0.94 (0.77-1.14)	0.93 (0.76-1.14)	1363	20,067	112	1252	1.06 (0.84-1.32)	1.10 (0.84-1.43)
≥ 75 years	1177	8613	115	897	0.99 (0.82-1.21)	1.05 (0.86-1.29)	840	5834	92	520	1.01 (0.81-1.26)	1.01 (0.81-1.27)
P for interaction					0.71	0.40					0.77	0.63
TSH												
0.45-4.49 mIU/L	2600	58,637			1 (ref)	1 (ref)	2203	25,901			1 (ref)	1 (ref)
4.50-6.99 mIU/L			168	2696	0.99 (0.85-1.16)	1.02 (0.87-1.20)			148	1229	1.11 (0.91-1.35)	1.13 (0.91-1.39)
7.00-9.99 mIU/L			38	676	0.92 (0.67-1.27)	1.01 (0.63-1.62)			37	344	1.04 (0.75-1.44)	1.09 (0.77-1.53)
10-19.99 mIU/L			23	365	1.17 (0.78-1.76)	1.22 (0.80-1.87)			18	183	0.88 (0.48-1.62)	0.93 (0.52-1.67)
P for trend					0.54	0.40					0.64	0.78
	Non-spine fracture [c]						**Spine fracture [d]**					
Total population	1745	21,722	166	1473	1.06 (0.90-1.24)	1.12 (0.91-1.38)	255	20,328	24	1431	0.96 (0.59-1.55)	1.00 (0.59-1.71)
Sex												
Men	592	10,326	40	569	0.87 (0.63-1.20)	0.88 (0.63-1.21)	106	10,332	7	569	1.08 (0.46-2.52)	1.21 (0.45-3.24)
Women	1153	11,396	126	904	1.17 (0.96-1.42)	1.24 (0.97-1.60)	149	9996	17	862	1.11 (0.62-1.99)	1.13 (0.60-2.13)
P for interaction					0.13	0.11					0.96	0.91
Age [f]												
< 75 years	1218	18,707	101	1143	1.18 (0.89-1.56)	1.22 (0.89-1.67)	167	17,476	10	1106	0.85 (0.45-1.61)	0.85 (0.45-1.62)
≥75 years	480	2732	63	319	1.00 (0.77-1.30)	1.00 (0.77-1.31)	88	2852	14	325	1.61 (0.74-3.51)	1.41 (0.68-2.95)
P for interaction					0.40	0.34					0.21	0.31
TSH												
0.45-4.49 mIU/L	1745	21,722			1 (ref)	1 (ref)	255	20,328			1 (ref)	1 (ref)
4.50-6.99 mIU/L			121	1003	1.23 (0.94-1.60)	1.25 (0.95-1.65)			15	974	0.88 (0.51-1.52)	0.95 (0.50-1.82)
7.00-9.99 mIU/L			27	288	0.97 (0.66-1.42)	1.03 (0.64-1.66)			7	288	1.58 (0.76-3.29)	1.67 (0.80-3.47)
10-19.99 mIU/L			17	167	1.01 (0.60-1.70)	1.05 (0.63-1.76)			2	160	2.08 (0.66-6.49)	2.17 (0.73-6.44)
P for trend					0.80	0.96					0.13	0.10

Abbreviations: CI, confidence interval; HR, hazard ratio; TSH, thyroid-stimulating hormone.

[a] The PROSPER study was not included because follow-up data were only available for any fracture

[b] The HUNT, Cardiovascular Health Study, Sheffield and OPUS 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 non-spine 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.

[e] Adjusted for age, sex, body mass index and smoking status. Complete case analysis was used, as missing data rate was <3% and unlikely to introduce relevant bias into the multivariable models[15,16].

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

eTable 8: Sensitivity analyses on the association between subclinical hypothyroidism and the risk of fractures

	Hip fracture					Any fracture				
	Euthyroidism		Subclinical Hypothyroidism		HR (95% CI)	Euthyroidism		Subclinical Hypothyroidism		HR (95% CI)
	Events	Participants	Events	Participants		Events	Participants	Events	Participants	
All eligible studies										
Random-effects model	2600	58,637	229	3759	0.96 (0.83-1.10)	2203	25,901	204	1772	1.02 (0.89-1.18)
Fixed-effects model	2600	58,637	229	3759	0.96 (0.83-1.10)	2203	25,901	204	1772	1.02 (0.89-1.18)
Definition of Subclinical Hypothyroidism										
Excluding those with missing FT4	2600	58,637	206	3492	0.95 (0.82-1.10)	2203	25,901	138	1493	0.98 (0.83-1.17)
Medication use										
Excluding users of thyroid medication at baseline [a]	2480	56,878	207	3325	0.98 (0.85-1.13)	2113	25,177	179	1557	1.04 (0.89-1.21)
Excluding users of thyroid medication at baseline or during follow-up [a]	2447	56,605	173	2999	1.02 (0.87-1.19)	2092	25,043	157	1397	1.11 (0.94-1.30)
Excluding users of thyroid and thyroid-altering medication [a]	2407	55,519	201	3259	0.97 (0.83-1.12)	2048	24,649	175	1516	1.06 (0.90-1.23)
Excluding users of anti-osteoporotic medication at baseline [b]	2582	58,469	228	3745	0.96 (0.84-1.10)	2162	25,759	199	1759	1.03 (0.89-1.19)
Outcomes										
Only studies with formal adjudication procedures [c]	2078	51,255	139	2698	0.93 (0.78-1.10)	1568	18,420	175	1342	1.00 (0.85-1.18)
Only studies with most uniform definition of fracture	2600	58,637	229	3759	0.96 (0.83-1.10)	1650	22,383	156	1576	0.97 (0.82-1.15)
Excluded Studies										
Excluding study inconsistent with proportional hazard assumption [d]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Excluding small study because of potential publication bias [e]	2594	57,465	229	3747	0.95 (0.83-1.09)	NA	NA	NA	NA	NA
Excluding studies with >5% loss to follow-up [f]	2528	55,299	222	3353	0.97 (0.84-1.12)	NA	NA	NA	NA	NA
Excluding studies with less objective outcome ascertainment [g]	2534	56,471	222	3365	0.97 (0.85-1.12)	1806	20,783	174	1466	1.01 (0.86-1.18)
Further adjustments of multivariable models										
Plus history of diabetes mellitus at baseline	2457	55,746	216	3631	0.98 (0.85-1.13)	2163	25,442	203	1745	1.06 (0.90-1.24)
	Non-spine fracture					**Spine fracture**				
All eligible studies										
Random-effects model	1745	21,722	166	1473	1.06 (0.90-1.24)	255	20,328	24	1431	0.96 (0.59-1.55)
Fixed-effects model	1745	21,722	166	1473	1.06 (0.90-1.24)	255	20,328	24	1431	0.92 (0.60-1.40)
Definition of Subclinical Hypothyroidism										
Excluding those with missing FT4	1745	21,722	106	1207	1.03 (0.81-1.31)	255	20,328	13	1165	0.92 (0.52-1.62)
Medication use										
Excluding users of thyroid medication at baseline [a]	1675	21,137	143	1304	1.05 (0.88-1.25)	240	19,745	21	1263	1.06 (0.59-1.91)
Excluding users of thyroid medication at baseline or during follow-up [a]	1660	21,030	125	1163	1.13 (0.93-1.38)	236	19,645	18	1130	1.16 (0.66-2.04)
Excluding users of thyroid and thyroid-altering medication [a]	1617	20,634	140	1269	1.06 (0.89-1.26)	232	19,242	20	1228	1.07 (0.58-1.96)
Excluding users of anti-osteoporotic medication at baseline [b]	1703	21,567	161	1461	1.06 (0.90-1.25)	245	20,191	22	1419	0.97 (0.56-1.68)
Outcomes										
Only studies with formal adjudication procedures [c]	1583	19,827	153	1385	1.05 (0.88-1.27)	239	18,421	23	1342	0.99 (0.57-1.74)
Only studies with most uniform definition of fracture	1596	20,315	156	991	1.02 (0.86-1.20)	174	16,810	16	1235	0.89 (0.45-1.79)
Excluded Studies										
Excluding study inconsistent with proportional hazard assumption [d]	NA	NA	NA	NA	NA	190	18,717	17	1324	0.82 (0.47-1.43)
Excluding small study because of potential publication bias [e]	NA	NA	NA	NA	NA	245	19,262	23	1398	0.90 (0.55-1.45)
Excluding studies with >5% loss to follow-up [f]	1646	20,600	166	1461	1.07 (0.90-1.27)	NA	NA	NA	NA	NA
Excluding studies with less objective outcome ascertainment [g]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Further adjustments of multivariable models										
Plus history of diabetes mellitus at baseline	1610	20,163	165	1 437	1.13 (0.92-1.40)	252	19,889	24	1407	1.01 (0.59-1.72)

Abbreviations: CI, confidence interval; FT4, free thyroxine; HR, hazard ratio (all age and sex adjusted, except for the last row); NA, data not applicable (no cohorts concerned by this sensitivity analysis).

[a] Thyroid medication includes thyroxine and anti-thyroid drugs; thyroid-altering medication includes oral corticosteroids, amiodarone and iodine.

[b] Anti-osteoporotic medication includes bisphosphonates, calcitonin, selective estrogen receptor modulator, parathyroid hormone.

[c] Formal adjudication procedures were defined as having clear criteria for the outcomes that were reviewed by experts for each potential case, which was performed in 8 studies.

[d] Excluding the Rotterdam study for spine fracture outcome.

[e] Excluding the Osteoporosis and Ultrasound Study (OPUS) for hip fracture outcome (p=0.57), and Invecchiare in Chianti Study (InChianti) for spine fracture outcome (p=0.21).

[f] Excluding the Osteoporosis and Ultrasound study and the Nagasaki Adult Health Study.

[g] Excluding the PROSPER study and the Nagasaki Adult Health Study, which did not ascertain fractures with independent blind assessment or record linkage.

eTable 9: Analysis on the association of thyroid medication treatment and fracture risk (treated vs. untreated)

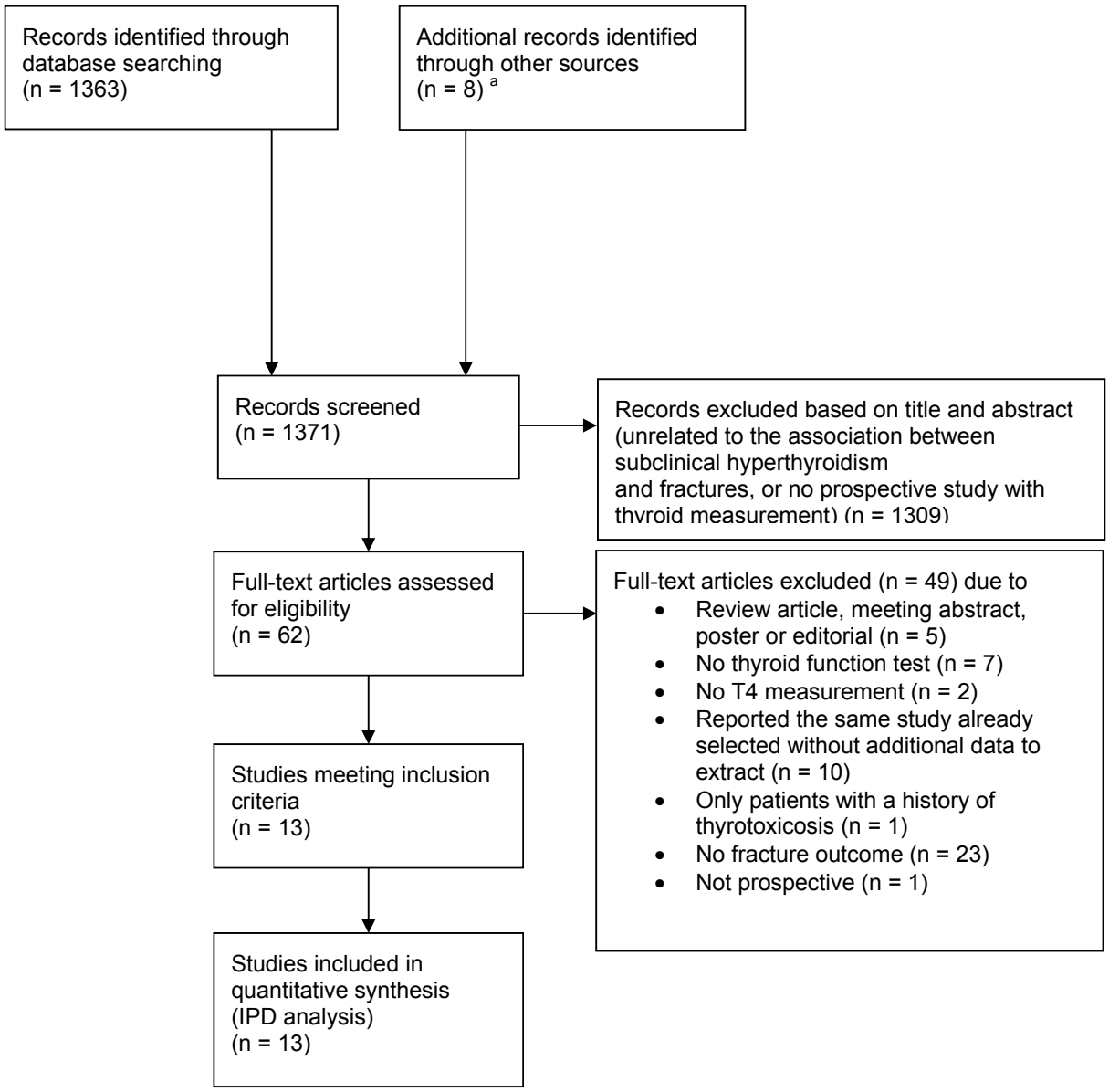
	Use of thyroid medication		No use of thyroid medication		Age and sex-adjusted HR (95% CI)
	Events	Participants	Events	Participants	
Hip fracture	200	2781	2734	59,624	1.06 (0.92-1.23)
Any fracture	135	1092	2382	27,396	0.98 (0.82-1.17)
Non-spine fracture	109	900	1722	21,504	1.03 (0.85-1.26)
Spine fracture	22	900	272	21,518	1.18 (0.76-1.83)

Abbreviations: CI, confidence interval; HR, hazard ratio.

eFigure 1: Flow Chart of Studies Evaluated for Inclusion in the Individual Participant Data

Title: Flow Chart of Studies Evaluated for Inclusion in the Individual Participant Data (IPD) Analysis, adapted from the Flow Diagram in the PRISMA Statement[18] and from [19].

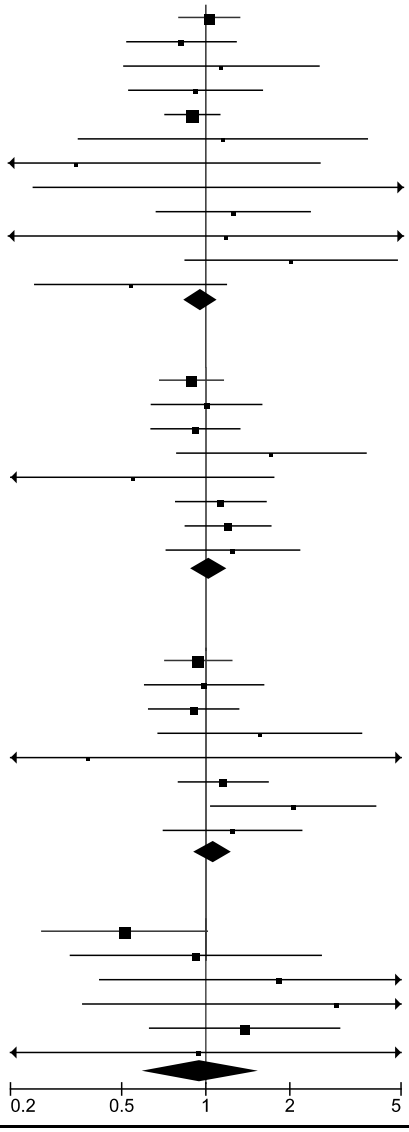
Legend: [a] from prospective cohorts already participating to the Thyroid Studies Collaboration that confirmed having prospective data on fracture outcomes.



eFigure 2: Forest plots of the association between subclinical hypothyroidism and the risk of fractures

Legend: Hip, any, non-spine and spine fractures in subclinical hypothyroidism vs. euthyroidism. Age and sex-adjusted hazard ratios (HR) and their 95% confidence intervals (CI) are represented by squares or diamonds. The sizes of the squares are proportional to the inverse of the variance of the HR. Not every outcome was available for each study. τ^2 measures heterogeneity in effect estimates across cohorts, with a pre-specified τ^2 of ≤0.04 representing low heterogeneity and >0.04 to <0.36 representing moderate heterogeneity. EPIC: European Prospective Investigation of Cancer. HUNT: Nord-Trøndelag Health Study.

Study	Euthyroidism Events, No.	Euthyroidism Participants, No.	Subclinical Hypothyroidism Events, No.	Subclinical Hypothyroidism Participants, No.	Forest plot	HR (95% CI)	Weight, %
Hip fracture							
Cardiovascular Health Study	378	2853	76	543		1.03 (0.80-1.31)	30.8
Health, Aging and Body Composition Study	171	2347	22	335		0.82 (0.53-1.28)	9.5
Osteoporotic Fractures in Men Study (MrOS)	51	1411	7	147		1.14 (0.51-2.51)	3
EPIC-Norfolk Study	189	11,986	14	720		0.92 (0.53-1.58)	6.3
HUNT Study	1507	31377	82	1313		0.90 (0.72-1.12)	37.8
Invecchiare in Chianti Study	45	1066	3	33		1.15 (0.35-3.72)	1.4
Leiden 85-Plus Study	34	456	1	35		0.35 (0.05-2.53)	0.5
Osteoporosis and Ultrasound Study (OPUS)	6	1172	0	12		5.68 (0.25-131)	0.2
Rotterdam Study	106	1611	11	107		1.25 (0.67-2.34)	4.8
Sheffield Study	3	285	0	31		1.18 (0.04-37.1)	0.2
Busselton Health Study	44	1907	6	89		2.00 (0.84-4.75)	2.5
Nagasaki Adult Health Study	66	2166	7	394		0.54 (0.25-1.18)	3.1
Total (τ^2 = 0.00)	**2600**	**58,637**	**229**	**3759**		**0.96 (0.83-1.10)**	**100**
Any fracture							
Health, Aging and Body Composition Study	463	2347	64	335		0.89 (0.68-1.15)	30.4
Osteoporotic Fractures in Men Study (MrOS)	186	1411	21	147		1.00 (0.64-1.58)	10.1
EPIC-Norfolk Study	453	11,985	31	720		0.92 (0.64-1.32)	15.7
Invecchiare in Chianti Study	87	1066	7	33		1.71 (0.79-3.74)	3.4
Leiden 85-Plus Study	64	456	3	35		0.55 (0.17-1.75)	1.6
PROSPER Study	397	5118	30	306		1.13 (0.78-1.64)	15.1
Rotterdam Study	379	1611	34	107		1.20 (0.84-1.71)	16.8
Busselton Health Study	174	1907	14	89		1.25 (0.72-2.16)	6.9
Total (τ^2 = 0.01)	**2203**	**25,901**	**204**	**1772**		**1.02 (0.89-1.18)**	**100**
Non-spine fracture							
Health, Aging and Body Composition Study	400	2347	58	335		0.94 (0.71-1.24)	33.9
Osteoporotic Fractures in Men Study (MrOS)	161	1411	18	147		0.99 (0.60-1.61)	10.8
EPIC-Norfolk Study	444	11,985	30	720		0.90 (0.62-1.31)	18.8
Invecchiare in Chianti Study	80	1066	6	33		1.56 (0.67-3.61)	3.7
Osteoporosis and Ultrasound Study (OPUS)	99	1122	0	12		0.38 (0.02-6.20)	0.3
Rotterdam Study	349	1611	31	107		1.15 (0.80-1.67)	19
Sheffield Study	50	285	10	31		2.05 (1.04-4.05)	5.6
Busselton Health Study	162	1895	13	88		1.24 (0.70-2.20)	8
Total (τ^2 = 0.00)	**1745**	**21,722**	**166**	**1473**		**1.06 (0.90-1.24)**	**100**
Spine fracture							
Health, Aging and Body Composition Study	109	2347	9	335		0.51 (0.26-1.01)	34.1
Osteoporotic Fractures in Men Study (MrOS)	39	1411	4	147		0.92 (0.33-2.59)	18
EPIC-Norfolk Study	16	11,986	2	720		1.83 (0.42-8.05)	9.6
Invecchiare in Chianti Study	10	1066	1	33		2.93 (0.36-23.6)	5
Rotterdam Study	65	1611	7	107		1.38 (0.63-3.01)	27.9
Busselton Health Study	16	1907	1	89		0.94 (0.12-7.20)	5.3
Total (τ^2 = 0.06)	**255**	**20,328**	**24**	**1431**		**0.96 (0.59-1.55)**	**100**



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