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ORIGINAL ARTICLE

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Association of subclinical thyroid dysfunction with bone mineral density and fracture: a meta-analysis of prospective cohort studies

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Abstract

Purpose To comprehensively investigate the associations of subclinical thyroid dysfunction with BMD and fractures at various sites.

Methods Comprehensive electronic and manual searches of databases were systematically conducted to identify prospective cohort studies from the inception of the databases to May 2019. The summary results for fractures and BMDs at various sites were calculated by relative risks (RRs) and weighted mean differences (WMDs) with corresponding 95% confidence intervals (CIs) using the random-effects model.

Results Seventeen prospective cohorts from 24 studies were identified and 313,557 individuals were recruited in a final analysis. The summary RR indicated that subclinical hyperthyroidism was associated with an increased risk of any fracture (RR, 1.17; 95% CI, 1.08–1.26; $P < 0.001$), hip fracture (RR, 1.27; 95% CI, 1.09–1.48; $P = 0.003$), spine fracture (RR, 1.97; 95% CI, 1.31–2.97; $P = 0.001$), and non-spine fracture (RR, 1.19; 95% CI, 1.04–1.37; $P = 0.014$). However, there were no significant associations of subclinical hypothyroidism with the risk of any fractures ($P = 0.166$), hip fracture ($P = 0.068$), spine fracture ($P = 0.818$), and non-spine fracture ($P = 0.277$). Finally, subclinical hyperthyroidism was associated with lower distal forearm BMD in women, and ultradistal forearm BMD in both men and women, whereas subclinical hypothyroidism was associated with higher femur neck BMD in women.

Conclusion Subclinical hyperthyroidism could induce additional risk on fractures at any, hip, spine, and non-spine, whereas subclinical hypothyroidism did not have any impact on fractures. Moreover, BMD at the lower distal and ultradistal forearms might be affected by subclinical hyperthyroidism, and higher femur neck BMD could be affected by subclinical hypothyroidism.

Keywords Subclinical thyroid dysfunction · Bone mineral density · Fracture · Meta-analysis

Introduction

Osteoporotic fractures, which are associated with significant functional disability, morbidity, mortality, and reduction in quality of life, are expected to increase worldwide [1–3]. There were nearly 10 million adults aged ≥50 years diagnosed with osteoporosis, and an additional 33 million with low bone mass, which was associated with an increased risk of fractures at various sites, in the US according to the National Osteoporosis Foundation [4]. Nowadays, numerous risk factors of fractures have already been identified, including bone mineral density (BMD), low body mass, sedentary lifestyle, type of fall, fracture history, smoking, and alcohol intake. Moreover, the association of overt hyperthyroidism with the risk of osteoporosis and fractures have already identified [5]. However, the prevalence of subclinical thyroid dysfunction is significantly higher than overt hyperthyroidism and hypothyroidism, and its impacts on subsequently fracture and BMD at various sites should been evaluated [6, 7].

Studies have already illustrated that individuals with subclinical thyroid dysfunction were associated with an increased risk of fractures, and the prevalence of fractures

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was increased when thyroid-stimulating hormone was reduced from the reference range [8]; however, these associations did not persist. Although numerous systematic reviews and meta-analyses have already conducted to evaluate the relation between subclinical thyroid dysfunction and fracture or BMD at various sites, these studies just pooled the data from individual studies and updated the pooled conclusion [9–14]. However, whether these associations differ according to the patients' characteristics remain limited and inconclusive. Therefore, the current meta-analysis was conducted based on a prospective cohort study to systematically explore any potential impacts of subclinical thyroid dysfunction (including subclinical hyperthyroidism and subclinical hypothyroidism) on fracture and BMD at various sites. Moreover, the relationship between subclinical thyroid dysfunction and fractures at various sites according to age, sex, cutoffs of the subclinical hyperthyroidism and subclinical hypothyroidism definitions, follow-up duration, and the relation between subclinical thyroid dysfunction and BMD at various sites according to sex were also illustrated.

Methods

Data sources, search strategy, and selection criteria

This comprehensive systematic review and meta-analysis was carried out and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement [15]. Studies that were designed as prospective cohort studies and evaluated the associations of subclinical hyperthyroidism or subclinical hypothyroidism with the fracture and BMD at various sites was eligible in this meta-analysis. Furthermore, there were no restrictions on the published language and status of the status. The electronic searches were placed on PubMed, EmBase, and the Cochrane library, and the cutoff date for searching data was May 2019. The core search terms included ("thyroid" OR "thyrotropin" OR "hyperthyroidism" OR "Hypothyroidism") AND ("bone mineral density" OR "fracture") AND "human". The reference lists of retrieved studies were also searched manually to identify any new eligible study.

The literature search and study selection were independently carried out by two reviewers, and any disagreement was settled by group discussion. The inclusion criteria of this meta-analysis are as follows: (1) study design, prospective cohort study; (2) participants, individuals who did not present fractures at baseline; (3) exposure and control, subclinical hyperthyroidism or subclinical hypothyroidism compared with normal thyroid-stimulating hormone; (4) outcomes, the study should have reported at least one of the following outcomes: any fracture, hip fracture, spine fracture, non-spine fracture, and BMD at various sites. If the study reported several multivariable adjusted effect estimates, we selected the effect estimate that was maximally adjusted for potential confounders.

Data collection and quality assessment

Two independent reviewers performed the data extraction and quality assessment, and conflicts were resolved by group discussion by referring to the original articles until a consensus was reached. The collected data items included the first author and study groups' name, publication year, country, sample size, mean age, percentage male, cutoff values of subclinical hypothyroidism and subclinical hyperthyroidism, thyroid medication, follow-up duration, adjusted factors, and investigated outcomes. The quality of the included studies was evaluated using the Newcastle-Ottawa Scale (NOS), which is a comprehensive and partially validated method for assessing the quality of observational study in a meta-analysis [16]. A "star system" of NOS to evaluate the quality of the observational study ranged from 0–9, and studies with 7–9 stars were considered as high quality.

Statistical analysis

The associations of subclinical hyperthyroidism and subclinical hypothyroidism with the risk of any fracture, hip fracture, spine fracture, non-spine fracture were assessed through effect estimates and 95% confidence intervals (CIs) in each included study, and the pooled relative risks (RRs) with its 95% CIs were calculated using the random-effects model [17, 18]. Moreover, the impacts of subclinical hyperthyroidism and subclinical hypothyroidism on BMD at various sites were calculated using weighted mean difference (WMD) and its 95% CI, and the pooled analysis using the random-effects model [17, 18]. Heterogeneity across the included studies were assessed using the I-square and P-value by Q statistic, and I-square > 50.0% or $P < 0.10$ was regarded as significant heterogeneity [19, 20]. Sensitivity analyses were conducted to assess the stability of the pooled conclusion and the impacts of single studies from the overall analysis [21]. After this, subgroup analyses for the risk of fracture at various sites were conducted based on age, sex, cutoff of subclinical hyperthyroidism and subclinical hypothyroidism definition, and follow-up duration. Moreover, the results of BMD at various sites between subclinical thyroid dysfunction and normal thyroid-stimulating hormone were calculated and stratified by sex. Next, the interaction test was conducted to compare differences between estimates of the two subgroups based on the Student's t distribution rather than on a normal distribution [22]. Publication biases for the investigated

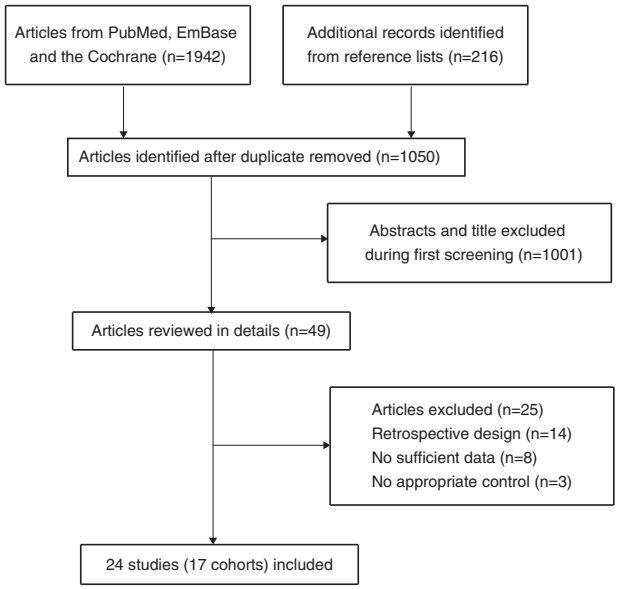

Fig. 1 Flow diagram of the literature search and study selection process

outcomes were calculated using the funnel plots, Egger, and Begg test analyses [23, 24]. The *P*-value for all pooled results are two-sided, and $P < 0.05$ was considered as statistically significant. All the statistical analyses in this study were conducted using the STATA software (version 12.0; Stata Corporation, College Station, TX, USA).

Results

Literature search

The details of the study selection process are presented in Fig. 1. The electronic searches produced 1942 records, and 892 were excluded due to duplicate topics. Moreover, 1001 articles were excluded due to irrelevant topics, and 49 studies were selected for full-text evaluations. After detailed evaluations, 17 prospective cohorts from 24 studies were selected for the final meta-analysis [25–48]. A manual search of the reference lists of these studies did not yield any new eligible studies. The baseline characteristics of the included studies and enrolled patients are summarized in Table 1.

Study characteristics

Seventeen prospective cohorts from 24 studies that recruited a total of 313,557 individuals were included. These studies were published between 2001 and 2014, and 367–231,355 participants were included in each cohort. The mean age of the included patients ranged from 51.0 to 85.0 years, and the follow-up duration ranged from 3.20 to 20.20 years. The cutoff values of subclinical hypothyroidism ranged from 3.50 to 5.50, and the cutoff values of subclinical hyperthyroidism ranged from 0.30 to 0.55. Sixteen cohorts were reported in western countries, and one cohort was reported in an eastern country. The NOS of the included studies ranged from 8 to 9, and all the studies were of high quality.

Any fracture

The breakdown for the number of studies available for the associations of subclinical hyperthyroidism and subclinical hypothyroidism with the risk of any fracture included 11 and 10 cohorts, respectively. We noted that subclinical hyperthyroidism was associated with an increased risk of any fracture (RR, 1.17; 95% CI, 1.08–1.26; $P < 0.001$; with no evidence of heterogeneity; Fig. 2), whereas subclinical hypothyroidism was not associated with the risk of any fracture (RR, 1.14; 95% CI, 0.95–1.38; $P = 0.166$; with significant heterogeneity; Fig. 2). The relation between subclinical hyperthyroidism and subclinical hypothyroidism with the risk of any fracture were not statistically significant ($P = 0.941$). Sensitivity analyses indicated that these conclusions were stable and not altered by sequential excluding of the individual cohort (Online Resource 1). No significant publication biases for the impacts of subclinical hyperthyroidism (*P*-value for Egger: 0.375; *P*-value for Begg: 0.876) and subclinical hypothyroidism (*P*-value for Egger: 0.644; *P*-value for Begg: 0.721) on the risk of any fractures (Online Resource 2).

Hip fracture

The breakdown for the number of studies available for the associations of subclinical hyperthyroidism and subclinical hypothyroidism with the risk of hip fracture included 13 and 13 cohorts, respectively. The pooled RR suggested subclinical hyperthyroidism produce an excess risk of hip fracture (RR, 1.27; 95% CI, 1.09–1.48; $P = 0.003$; with no evidence of heterogeneity; Fig. 3), whereas there was no significant association between subclinical hypothyroidism and hip fracture (RR, 1.14; 95% CI, 0.99–1.31; $P = 0.068$; with unimportant heterogeneity; Fig. 3). The differences for the potential impacts of subclinical hyperthyroidism or subclinical hypothyroidism on the risk of hip fracture were not statistically significant ($P = 0.283$). The summary conclusion for the relation between subclinical hyperthyroidism and hip fracture risk was stable, whereas for subclinical hypothyroidism was variable due to marginal 95% CI (Online Resource 1). No significant publication biases for the relation of subclinical hyperthyroidism (*P*-value for Egger: 0.303; *P*-value for Begg: 0.760) or subclinical hypothyroidism (*P*-value for Egger: 0.862; *P*-value for Begg: 0.760) with the risk of hip fracture (Online Resource 2).

Table 1 Baseline characteristic of studies included in the systematic review and meta-analysis

Study	Publication year	Country	Sample size	Mean age (years)	Percentage male (%)	Cutoff value of SH	Cutoff value of SCH	Thyroid medication (%)	Follow-up (year)	Adjusted factors	NOS score
Bauer (SOF) [25]	2001	USA	686	72.0	0.0	>5.50	<0.50	11.0	5.9	Age, use of thyroid hormone, previous hyperthyroidism, good or excellent self-rated health, current oral estrogen use	9
Imaizumi (RERF) [26]	2004	Japan	2762	57.0	39.0	>4.50	<0.45	1.4	20.2	Age, gender, BMI, smoking status, history of DM, thyroid medication	8
Gussekloo (Leiden 85-Plus) [27]	2004	Netherlands	558	85.0	34.0	>4.50	<0.45	4.0	4.9	Age, gender, BMI, smoking status, history of DM, thyroid and thyroid-altering medication, anti-osteoporotic medication	8
Rodondi (Health-ABC) [28, 29]	2005	USA	2.764	74.7	49.1	>4.50	<0.45	9.7	12.8	Age, gender, BMI, smoking status, history of DM, thyroid and thyroid-altering medication, anti-osteoporotic medication	8
Walsh (BHS) [30]	2005	Australia	2049	51.0	50.9	>4.50	<0.45	0.9	20.0	Age, gender, BMI, smoking status, history of DM, thyroid medication, anti-osteoporotic medication	8
van der Deure (Rotterdam) [31–33]	2008	Netherlands	1838	69.0	38.7	>4.30	<0.40	2.3	9.4	Age, gender, BMI, smoking status, history of DM, thyroid medication	9
Grimnes (Tromsø) [34]	2008	Norway	1961	63.7	49.4	>4.56	<0.49	NA	NA	Age, weight, height, physical activity score, and current smoking	8
Finigan [35]	2008	UK	367	64.6	0.0	NA	NA	NA	10.0	Age, bone mineral density	8
Flynn (TEARS) [36, 37]	2010	Scotland	17,684	60.5	14.1	>4.00	<0.40	Yes	4.5	Age, sex, history of hyperthyroidism, history of osteoporotic fracture, DM	9

Table 1 (continued)

Study	Publication year	Country	Sample size	Mean age (years)	Percentage male (%)	Cutoff value of SH	Cutoff value of SCH	Thyroid medication (%)	Follow-up (year)	Adjusted factors	NOS score
Lee (CHS) [38, 39]	2010	USA	3567	72.8	38.5	>4.50	<0.45	9.2	13.0	Age, race, self-reported health status, frailty status, smoking, alcohol use, height, weight, and calcium supplementation, thyroid and thyroid-altering medication, anti-osteoporotic medication	9
Boekholdt (EPICNorfolk) [40]	2010	UK	13,066	58.0	45.6	>4.50	<0.45	3.4	12.4	Age, gender, BMI, smoking status, history of DM, thyroid and thyroid-altering medication	8
Murphy (OPUS) [41]	2010	Five European cities	1433	63.0	0.0	>4.50	<0.45	0.0	6.0	Age, gender, BMI, smoking status, thyroid and thyroid-altering medication, anti-osteoporotic medication	8
Nanchen (PROSPER) [42]	2012	Netherlands, Scotland, and Ireland	5563	75.0	49.2	>4.50	<0.45	3.3	3.2	Age, gender, BMI, smoking status, history of DM, thyroid and thyroid-altering medication	8
Svare (HUNT2) [43]	2013	Norway	25,205	58.2	34.1	>3.50	<0.50	4.7	12.5	Age, gender, BMI, smoking status, history of DM, thyroid or thyroid-altering medication	8
Waring (MrOS) [44, 45]	2013	USA	1513	73.0	100.0	>4.78	<0.55	7.6	8.6	Age, clinic site, race, BMI, physical activity score, alcohol intake, smoking status, corticosteroid use, and thyroid hormone use	8
Ceresini (InCHIANTI) [46]	2013	Italy	1186	71.0	44.0	>4.50	<0.45	2.4	9.1	Age, gender, BMI, smoking status, history of DM, thyroid and thyroid-altering	8

Table 1 (continued)

Study	Publication year	Country	Sample size	Mean age (years)	Percentage male (%)	Cutoff value of SH	Cutoff value of SCH	Thyroid medication (%)	Follow-up (year)	Adjusted factors	NOS score
										medication, anti-osteoporotic medication	
Abrahamsen (OPENTHYRO) [47, 48]	2014	Denmark	231,355	61.9	50.1	>5.00	<0.30	NA	7.5	Age, sex, Charlson index, prednisolone in last year, osteoporosis treatment in last year, diabetes, dementia, heart failure, malignancy, liver disease, rheumatic diseases, pulmonary disease, prior major osteoporotic fracture, year, site	9

BMI body mass index, *DM* diabetes mellitus, *SCH* subclinical hyperthyroidism, *SH* subclinical hypothyroidism

Spine fracture

The breakdown for the number of studies available for the associations of subclinical hyperthyroidism and subclinical hypothyroidism with the risk of spine fracture was 7 cohorts and 6 cohorts, respectively. We noted that subclinical hyperthyroidism was associated with an increased risk of spine fracture (RR, 1.97; 95% CI, 1.31–2.97; $P = 0.001$; with no evidence of heterogeneity; Fig. 4), whereas no significant association between subclinical hypothyroidism and spine fracture was detected (RR, 0.95; 95% CI, 0.63–1.44; $P = 0.818$; with no evidence of heterogeneity; Fig. 4). We noted significant difference regarding the associations of subclinical hyperthyroidism and subclinical hypothyroidism with the risk of spine fracture ($P = 0.014$). Sensitivity analyses indicated these conclusions were stable and not altered by any single cohort (Online Resource 1). There was no significant publication bias for the relation between subclinical hyperthyroidism (*P*-value for Egger: 0.382; *P*-value for Begg: 0.548) or subclinical hypothyroidism (*P*-value for Egger: 0.201; *P*-value for Begg: 0.452) and the risk of spine fracture (Online Resource 2).

Non-spine fracture

The breakdown for the number of studies available for the associations of subclinical hyperthyroidism and subclinical hypothyroidism with the risk of non-spine fracture was 10 cohorts and 8 cohorts, respectively. We noted subclinical hyperthyroidism produce additional risk of non-spine fracture (RR, 1.19; 95% CI, 1.04–1.37; $P = 0.014$; with no evidence of heterogeneity; Fig. 5), whereas subclinical hypothyroidism was not associated with the risk of non-spine fracture (RR, 1.09; 95% CI, 0.93–1.27; $P = 0.277$; with no evidence of heterogeneity; Fig. 5). The relation between subclinical hyperthyroidism and subclinical hypothyroidism with the risk of non-spine fracture was not associated with statistically significant ($P = 0.406$). The results of sensitivity analyses indicated these conclusions are stable and not changed by sequential excluding included cohorts (Online Resource 1). No significant publication biases for subclinical hyperthyroidism (*P*-value for Egger: 0.605; *P*-value for Begg: 0.858) and subclinical hypothyroidism (*P*-value for Egger: 0.561; *P*-value for Begg: 0.536) with the risk of non-spine fracture (Online Resource 2).

Subgroup analysis

The results of subgroup analyses for the associations of subclinical hyperthyroidism with the risk of fracture at various sites are shown in Table 2. Although subclinical hyperthyroidism was associated with an increased risk of any fracture, hip fracture, spine fracture, and non-spine

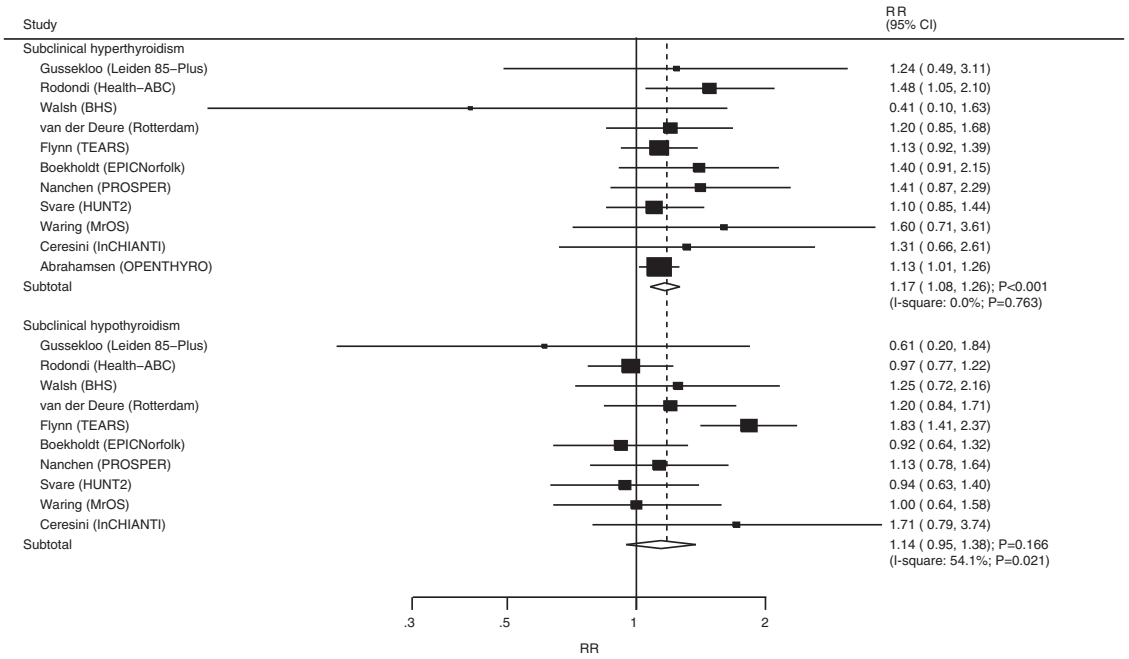

Fig. 2 Associations of subclinical hyperthyroidism and subclinical hypothyroidism with the risk of any fracture

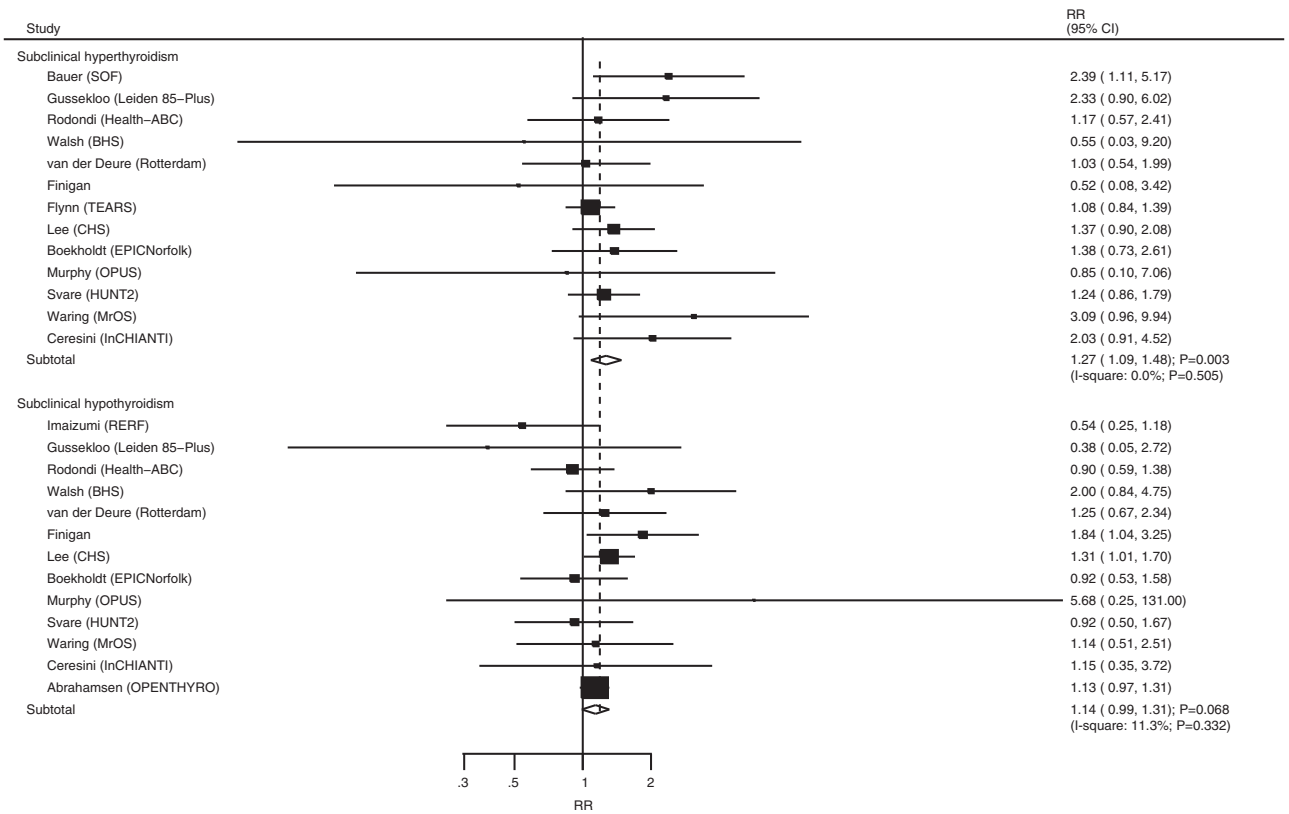

Fig. 3 Associations of subclinical hyperthyroidism and subclinical hypothyroidism with the risk of hip fracture

fracture in mostly subsets, we noted no significant association between subclinical hyperthyroidism and any fracture risk when study just included men, and follow-up duration ≥ 10.0 years. Moreover, there was no significant association between subclinical hyperthyroidism and the risk of hip fracture when the mean age of individuals < 70.0

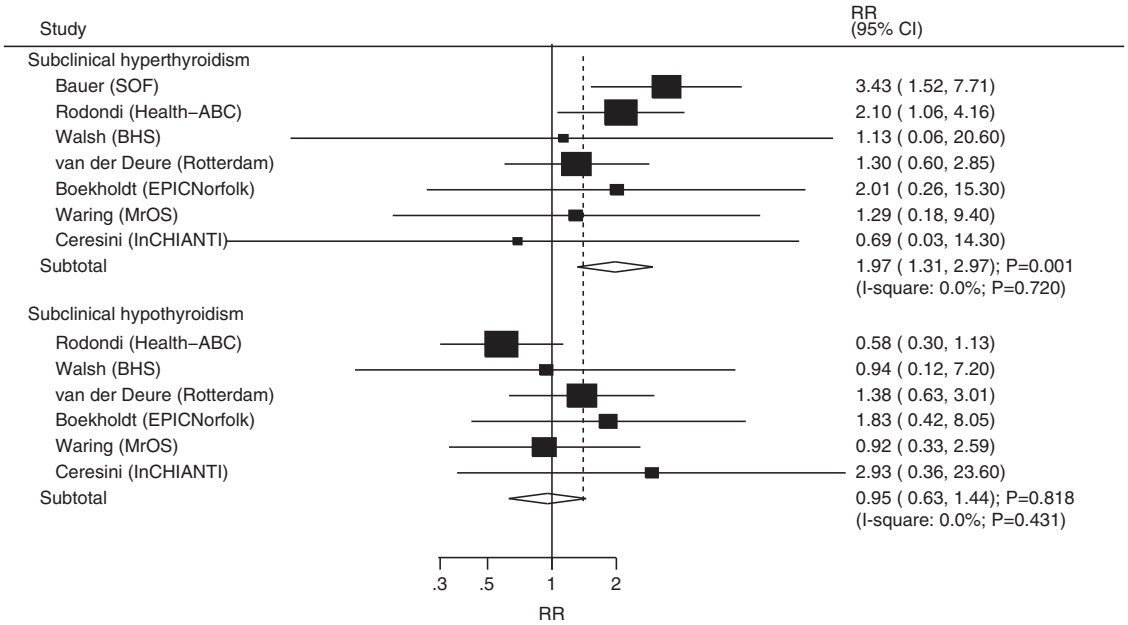

Fig. 4 Associations of subclinical hyperthyroidism and subclinical hypothyroidism with the risk of spine fracture

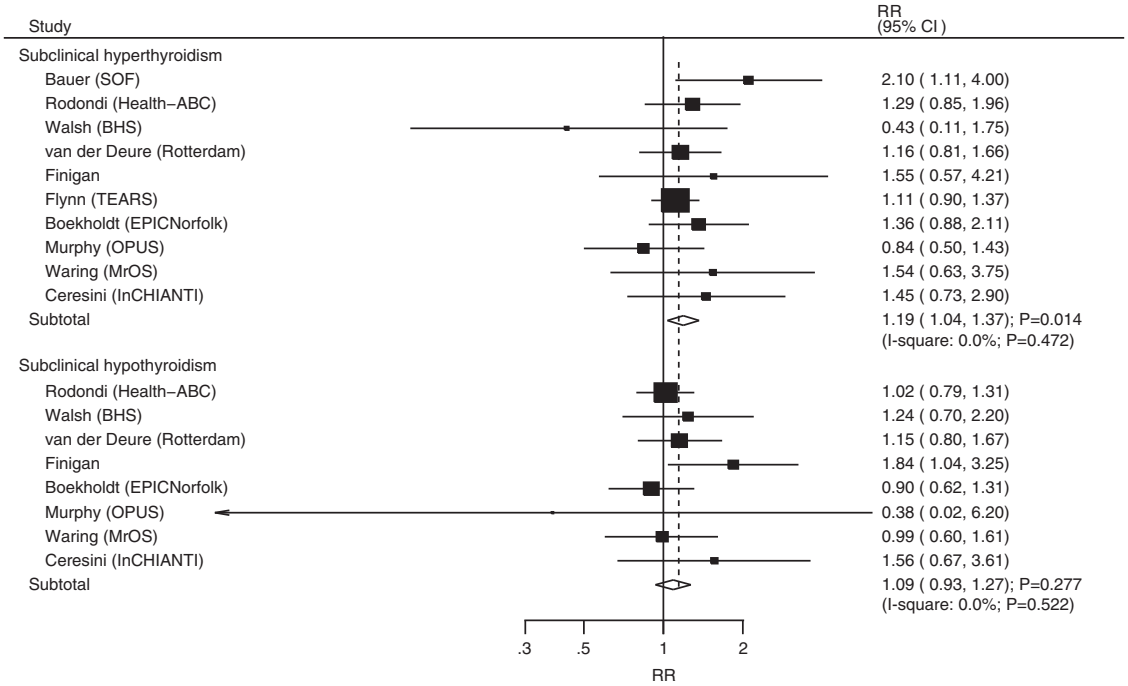

Fig. 5 Associations of subclinical hyperthyroidism and subclinical hypothyroidism with the risk of non-spine fracture

years, study just included men, used other cutoff value of subclinical hyperthyroidism, and follow-up duration ≥ 10.0 years. Furthermore, subclinical hyperthyroidism was not associated with the risk of spine fracture if the mean age of individuals < 70.0 years, study just included men, and used other cutoff value of subclinical hyperthyroidism. Additionally, no significant association of subclinical hyperthyroidism with the risk of non-spine fracture when the mean age of individuals < 70.0 years, the study just included men or women, the study used 0.45 as cutoff value of subclinical hyperthyroidism, and irrespective follow-up duration. Finally, the associations of subclinical hyperthyroidism with the risk of hip fracture could affect by the participants' age ($P = 0.024$). The results of subgroup

Table 2 Subgroup analyses for the associations of subclinical hyperthyroidism with the risk of fractures at various sites

Fracture sites	Factor	Subgroup	Number of studies	RR and 95% CI	*P*-value	I^2 (%)	*P*-value for heterogeneity	*P*-value between subgroups
Any	Mean age (years)	≥70.0	5	1.43 (1.13–1.82)	0.003	0.0	0.992	0.074
		<70.0	6	1.14 (1.04–1.24)	0.003	0.0	0.681	
	Sex	Men	3	1.18 (0.94–1.47)	0.152	0.0	0.548	0.770
		Women	2	1.11 (1.00–1.24)	0.049	0.0	0.864	
		Both	9	1.17 (1.07–1.27)	<0.001	0.0	0.667	
	Cutoff value	<0.45	6	1.37 (1.11–1.70)	0.004	0.0	0.678	0.107
		Other	5	1.14 (1.04–1.24)	0.004	0.0	0.932	
	Follow-up (years)	≥10.0	4	1.24 (0.96–1.60)	0.097	33.5	0.211	0.519
		<10.0	7	1.15 (1.05–1.26)	0.002	0.0	0.948	
Hip	Mean age (years)	≥70.0	6	1.66 (1.25–2.20)	<0.001	0.0	0.495	0.024
		<70.0	7	1.13 (0.93–1.36)	0.215	0.0	0.938	
	Sex	Men	3	1.98 (0.87–4.50)	0.103	41.6	0.180	0.380
		Women	5	1.40 (1.03–1.91)	0.034	0.0	0.513	
		Both	8	1.22 (1.02–1.46)	0.031	0.0	0.631	
	Cutoff value	<0.45	7	1.44 (1.10–1.90)	0.009	0.0	0.840	0.262
		Other	6	1.26 (0.96–1.67)	0.099	31.2	0.201	
	Follow-up (years)	≥10.0	6	1.27 (1.00–1.60)	0.050	0.0	0.918	0.988
		<10.0	7	1.52 (1.07–2.18)	0.021	38.9	0.132	
Spine	Mean age (years)	≥70.0	4	2.38 (1.45–3.92)	0.001	0.0	0.595	0.204
		<70.0	3	1.36 (0.67–2.75)	0.395	0.0	0.919	
	Sex	Men	1	1.29 (0.18–9.32)	0.801	–	–	0.296
		Women	1	3.43 (1.52–7.73)	0.003	–	–	
		Both	5	1.66 (1.02–2.70)	0.040	0.0	0.871	
	Cutoff value	<0.45	4	1.94 (1.05–3.61)	0.035	0.0	0.893	0.948
		Other	3	1.97 (0.96–4.06)	0.065	34.6	0.217	
	Follow-up (years)	≥10.0	3	2.03 (1.08–3.82)	0.028	0.0	0.921	0.909
		<10.0	4	1.91 (1.03–3.53)	0.040	14.3	0.320	
Non-spine	Mean age (years)	≥70.0	4	1.49 (1.11–2.00)	0.008	0.0	0.666	0.090
		<70.0	6	1.12 (0.95–1.31)	0.168	0.0	0.522	
	Sex	Men	1	1.54 (0.63–3.76)	0.343	–	–	0.799
		Women	3	1.35 (0.72–2.52)	0.353	59.1	0.087	
		Both	6	1.17 (1.01–1.36)	0.041	0.0	0.655	
	Cutoff value	<0.45	5	1.17 (0.90–1.52)	0.255	12.6	0.334	0.903
		Other	5	1.20 (1.01–1.42)	0.038	1.1	0.400	
	Follow-up (years)	≥10.0	4	1.28 (0.96–1.70)	0.089	0.0	0.457	0.568
		<10.0	6	1.18 (0.98–1.42)	0.083	12.3	0.336	

Table 3 The results of previous meta-analyses

Study	Included studies	Total no. of participants	Main endpoints	Limitation
Yan et al. [9]	5	314,146	Unadjusted SH for fracture: 1.30; 95% CI: 1.08–1.56; adjusted SH for fracture 1.20; 95% CI: 0.70–2.04; Unadjusted SCH for fracture: 1.52; 95% CI: 1.33–1.73; adjusted SCH for fracture: 1.25; 95% CI: 1.11–1.41	The relationship of SCH or SH with the risk of fracture at various sites was not addressed
Aubert et al. [10]	13	56,835	Adjusted HR for hip fracture was 1.25 (95% CI: 1.05 to 1.49) for TSH 0.45 to 0.99 mIU/L, 1.19 (95%CI: 1.01 to 1.41) for TSH 1.00 to 1.49 mIU/L, 1.09 (95% CI: 0.93 to 1.28) for TSH 1.50 to 2.49 mIU/L, and 1.12 (95CI: 0.94 to 1.33) for TSH 2.50 to 3.49 mIU/L (P for trend = 0.004). Hip fracture was also associated with free thyroxine [HR (95% CI) 1.22 (1.11 to 1.35) per one standard deviation increase in free thyroxine]	Individuals with subclinical thyroid dysfunction and fractures at various sites were not evaluated
Blum et al. [11]	13	70,298	In age- and sex-adjusted analyses, the HR for SCH vs. euthyroidism was 1.36 for hip fracture (95% CI, 1.13–1.64); HR was 1.28 (95% CI, 1.06–1.53) for any fracture; HR was 1.16 (95% CI, 0.95–1.41) for non-spine fracture; HR was 1.51 (95% CI, 0.93–2.45) for spine fracture;	Several additional published articles were not entered in the pooled analysis
Segna et al. [12]	6	5458	SCH had a greater annual bone loss at the femoral neck vs. euthyroidism: %ΔBMD = –0.18 (95% CI: −0.34, −0.02), with a nonstatistically significant pattern at the total hip: %ΔBMD = −0.14 (95% CI: −0.38, 0.10), but not at the lumbar spine: %ΔBMD = 0.03 (95% CI: −0.30, 0.36); especially participants with TSH < 0.10 mIU/L showed an increased bone loss in the femoral neck (%Δ BMD = −0.59; [95% CI: −0.99, −0.19]) and total hip region (%ΔBMD = −0.46 [95% CI: −1.05, −0.13])	The results regarding stratified analyses were not conducted
Wirth et al. [13]	7	50,245	The pooled adjusted hazard ratios (HRs) of participants with SCH vs. euthyrodism were 1.38 (95% CI, 0.92 to 2.07) for hip fractures and 1.20 (CI, 0.83 to 1.72) for non-spine fractures	Numerous studies were not included
Yang et al. [14]	19	79,368	SH was associated with relative risks (RRs) of 1.34 (95% CI 1.14, 1.58) for hip fracture, 1.27 (95% CI 1.02, 1.58) for any fracture, and 1.25 (95% CI 1.04, 1.50) for forearm fracture. SCH was associated with RRs of 1.71 (95% CI 1.06, 2.76) for spine fracture, 1.20 (95% CI 1.03, 1.39) for non-spine fracture, 1.44 (95% CI 1.21, 1.71) for hip fracture, and 1.38 (95% CI 1.21, 1.58) for any fracture. The change in BMD at the hip (WMD: −0.060, 95% CI −0.116, −0.004) and femoral neck (WMD: −0.046, 95% CI −0.077, −0.015) was significantly decreased in the SCH compared with the euthyroidism groups in females	This study had a mistake due to the cardiovascular health study that duplicated the entered data. Whether these associations differ according to individuals' age, sex, cutoff value of SCH or SH, and follow-up duration were not evaluated.

SH subclinical hypothyroidism, *SCH* subclinical hyperthyroidism, *TSH* thyroid-stimulating hormone

analyses for the associations of subclinical hypothyroidism with the risk of fracture at various sites are shown in Online resource S3. We noted the no significant impacts of subclinical hypothyroidism on the risk of fracture at various sites in mostly subsets. However, we noted subclinical hypothyroidism was associated with an increased risk of hip fracture when used other cutoff value of subclinical hypothyroidism. Finally, we noted the association of subclinical hypothyroidism with the risk of any fracture could affect by cutoff value of subclinical hypothyroidism and follow-up duration.

BMD at various sites

The results for the impacts of subclinical hyperthyroidism or subclinical hypothyroidism on BMD at various sites are summarized in Online resource S4. We noted subclinical hypothyroidism was associated with an increased femur neck BMD in women (WMD: 0.04; 95% CI, 0.01 to 0.08; $P = 0.026$). Moreover, subclinical hyperthyroidism was associated with a reduced distal forearm BMD in women (WMD: −0.03; 95% CI, −0.05 to −0.00; $P = 0.039$). Furthermore, subclinical hyperthyroidism was associated with lower ultradistal forearm BMD in men (WMD: −0.03; 95% CI, −0.05 to −0.00; $P = 0.031$) and women (WMD: −0.03; 95% CI, −0.05 to −0.00; $P = 0.027$). No other significant difference was detected for the impacts of subclinical hyperthyroidism or subclinical hypothyroidism on BMD at other sites.

Discussion

The current meta-analysis of prospective cohort studies aimed to explore any potential correlations between subclinical hyperthyroidism or subclinical hypothyroidism and the outcomes of fracture and BMD at various sites. This comprehensive quantitative study included 313,557 individuals from 17 cohorts published in 24 studies with a wide range of individuals' characteristics. The results of this meta-analysis indicated that subclinical hyperthyroidism produces excess risk of any fracture, hip fracture, spine fracture, and non-spine fracture, whereas subclinical hypothyroidism was not associated with the risk of any fracture, hip fracture, spine fracture, and non-spine fracture. The BMD at the femur neck, distal forearm, and ultradistal forearm could be affected by subclinical hyperthyroidism or subclinical hypothyroidism. Finally, the individuals' age could affect the relationship between subclinical hyperthyroidism and hip fracture, whereas the relationship between subclinical hypothyroidism and any fracture could be affected by the cutoff of the subclinical hypothyroidism definition and follow-up duration.

The results and limitations of previous systematic reviews and meta-analyses have already presented in Table 3. The current updated meta-analysis was conducted based on prospective cohort studies to evaluate the relationship of subclinical hyperthyroidism or subclinical hypothyroidism with the risk of fracture and BMD at various sites to address the limitations of previous studies [9–14]. The summary results indicated that subclinical hyperthyroidism was associated with the excess risk of any fracture, hip fracture, spine fracture, and non-spine fracture, which was consistent with previous meta-analyses [9, 11, 14]. The included studies reported a positive trend for the impacts of subclinical hyperthyroidism on fractures at various sites. The potential reason for this significant association could be due to the follow mechanisms: (1) the direct impacts of thyroid hormones on osteoclasts, since subclinical hyperthyroidism was associated with low thyroid-stimulating hormone and produces greater bone turnover and bone loss [49, 50]; (2) individuals presented with subclinical hyperthyroidism could have decreased thigh muscle strength and thus a greater risk of fall-related fractures [51]; and (3) subclinical hyperthyroidism was associated with an increased risk of osteoporosis that caused vulnerabilities to fractures [52, 53]. The results of the subgroup analyses indicated that the relationship between subclinical hyperthyroidism and hip fracture could be affected by an individual's age. The potential reason for this could be the severity of osteoporosis. Furthermore, BMD could be affected by an individual's age, and the synthetic effects of age and low BMD could affect the relationship between subclinical hyperthyroidism and hip fracture.

The summary results of this study indicated no significant associations of subclinical hypothyroidism with the risk of any fracture, hip fracture, spine fracture, and non-spine fracture, which were inconsistent with previous meta-analysis [14]. The potential reasons for this included: (1) individuals with subclinical hypothyroidism were significantly correlated with bone metabolism disorders, whereas there were no significantly impacts on BMD levels at various sites [54]; and (2) the effects of exogenous and endogenous thyroid hormone differed due to different metabolic pathways [55]. Subgroup analyses indicated that subclinical hypothyroidism was associated with an increased risk of hip fracture when other cutoff values of thyroid-stimulating hormone were used. Moreover, cutoff values of subclinical hypothyroidism and follow-up duration could affect the relationship between subclinical hypothyroidism and the risk of any fracture. The potential reasons for this included: (1) the cutoff value could determine the categories of subclinical hypothyroidism and euthyroid, which could affect the absolute effect estimate for the relationship between subclinical hypothyroidism and fracture at various sites; and (2) the duration of follow-up

were significantly correlated with the background therapies, severity of disease, other chronic disease, and the number of events that occurred. Finally, we noted that subclinical hyperthyroidism induces low-distal forearm BMD in women, and ultradistal forearm BMD in men and women. Moreover, high femur neck BMD in women with subclinical hypothyroidism was observed. However, these results were not stable due to the smaller number of included studies that reported the impacts of subclinical hyperthyroidism and subclinical hypothyroidism on BMD at various sites.

Several limitations in this meta-analysis should be mentioned: (1) the adjusted factors were not consistent among included studies, which might affect the progression of fractures at various sites; (2) the cutoff values of subclinical hyperthyroidism and subclinical hypothyroidism could affect the absolute effect estimates for the assessed relationship between subclinical thyroid dysfunction and fracture risk; (3) the analysis on the basis of published articles and publication bias was inevitable; and (4) the individual data from the included studies were not available, which prevented us from conducting more detail stratified analyses.

In conclusion, the findings of this study suggested that subclinical hyperthyroidism was a potential risk factor on the incidences of any fracture, hip fracture, spine fracture, and non-spine fracture. However, subclinical hypothyroidism has no significant effects on the risk of any fracture, hip fracture, spine fracture, and non-spine fracture. Moreover, subclinical hyperthyroidism and subclinical hypothyroidism might play an important role on BMD at the femur neck, distal forearm, and ultradistal forearm. Finally, the associations of subclinical hyperthyroidism and subclinical hypothyroidism with the risk of any fracture and hip fracture might be affect by the individual's age, cutoff value, and follow-up duration.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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