Association between Subclinical Thyroid Dysfunction and Change in Bone Mineral Density in Prospective Cohorts

Running title: Thyroid Disease and Bone Loss

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Key terms: Thyroid Disease, Hypothyroidism, Hyperthyroidism, Bone Density, Bone Loss, Prospective Studies

Word count: 2,318

Abstract count (without subheadings): 239

Tables / Figures: 2/1

Online-only Tables/Figures: 4/2

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Abstract

Background: Subclinical hyperthyroidism (SHyper) has been associated with increased risk for hip and other fractures, but the linking mechanisms remain unclear.

Objective: To investigate the association between subclinical thyroid dysfunction and bone loss.

Methods: Individual participant data analysis after a systematic literature search in MEDLINE/EMBASE (1946-2016). Two reviewers independently screened and selected prospective cohorts providing baseline thyroid status and serial bone mineral density (BMD) measurements. We classified thyroid status as euthyroidism (thyroid-stimulating hormone [TSH] 0·45-4·49mIU/l), SHyper (TSH<0.45mIU/l) and subclinical hypothyroidism (SHypo, TSH≥4·50-19·99mIU/l) both with normal free thyroxine levels. Our primary outcome was annualized percentage BMD change (%ΔBMD) from serial dual x-ray absorptiometry scans of the femoral neck, total hip and lumbar spine, obtained from multivariable regression in a random-effects two-step approach.

Results: Among 5,458 individuals (median age 72 years, 49·1% women) from 6 prospective cohorts, 451 (8·3%) had SHypo and 284 (5·2%) had SHyper. During 36,569 person-years of follow-up, those with SHyper had a greater annual bone loss at the femoral neck vs. euthyroidism: %ΔBMD=-0·18 (95%CI:-0·34,-0·02; I^2=0%), with a non-statistically significant pattern at the total hip: %ΔBMD=-0·14 (95%CI:-0·38,0·10; I^2=53%), but not at the lumbar spine: %ΔBMD=0·03 (95%CI:-0·30,0·36; I^2=25%). Especially participants with TSH<0·10mIU/l showed an increased bone loss in the femoral neck (%ΔBMD=-0·59;[95%CI:-0·99,-0·19]) and total hip region (%ΔBMD=-0·46 [95%CI:-1·05,-0·13]). In contrast, SHypo was not associated with bone loss at any site.

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Conclusion: Among adults, SHyper was associated with increased femoral neck bone loss, potentially contributing to the increased fracture risk.

Introduction

Overt hyperthyroidism is a known risk factor for decreased bone mineral density (BMD) and fractures (1-3) whereas overt hypothyroidism is not, except during thyroxine overreplacement.(4) Compared to overt thyroid disease, subclinical thyroid dysfunction (SCTD) is a more common phenomenon, with a prevalence reaching 10% for subclinical hypothyroidism (SHypo) in the elderly (5) and 3·2% for subclinical hyperthyroidism (SHyper).(6)

Among 70,298 individual participant data (IPD) from prospective cohort studies, we found that SHyper (but not SHypo) was associated with an increased risk up to 36% of fractures compared to euthyroidism.(7)

Yet the underlying pathophysiologic mechanism remains unclear. Increased bone loss may mediate this association, and is best assessed with serial bone mineral density measurements to assess bone health and evaluate the future risk for osteoporotic fractures.(8, 9) However, data on the association between SCTD and bone loss are limited to one prospective cohort study conducted only in men.(10) To investigate the influence of SCTD on bone loss, a potential mediator in its association with fracture risk, we conducted a pooled IPD analysis from all population-based prospective cohort studies with baseline thyroid status and serial BMD assessments.

Methods

Search Strategy and Selection Criteria

We report this IPD analysis according to the PRISMA-IPD statement (11) and published the study protocol online in the International prospective register of meta-analyses (PROSPERO CRD42015019814).(12). We conducted a systematic literature search in EMBASE and

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Medline from inception until September, 5th, 2016 without language restrictions, and searched bibliographies of key articles in the field. We included IPD from prospective cohorts with available baseline thyroid status and serial BMD measurements. We excluded studies assessing individuals with overt thyroid dysfunction only, or limited to participants pre-treated for either thyroid or bone diseases. Two physicians (DS, CEA) independently assessed each study's eligibility (title and abstract screen: Cohen's kappa coefficient [κ]=0·80; full-text search: κ=1·00), potential risks of bias, and study quality using the Newcastle-Ottawa Quality Assessment Scale.(13) Remaining uncertainties were solved with a third author (NR). Furthermore, we included unpublished IPD from the Thyroid Studies Collaboration,(7) an international network of high-quality prospective cohort studies. In case of unclear data issues (e.g. unreasonable outliers), we contacted the designated cohort contact persons.

Thyroid Status

All cohorts measured TSH using third-generation assays, whereas fT4 assay kits varied across studies. Similar to previous IPD analyses,(7, 14, 15) we used uniform TSH cutoff levels based on an expert consensus meeting of the Thyroid Studies Collaboration, expert reviews,(16, 17) and cohort-specific cut-offs for fT4 reference ranges (Appendix Table 1) for a better comparability. We defined euthyroidism as TSH 0.45-4.49mIU/l, SHypo as TSH between 4.50-19.99mIU/l with fT4 within reference range, SHyper as TSH <0.45mIU/l with fT4 within reference range. We excluded individuals with overt hypothyroidism (n=124) and hyperthyroidism (n=90), as well as other discordant thyroid function tests due to unclear cause/mechanisms (n=27).

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Assessment of Bone- and Thyroid-Altering Medication

We collected data on anti-osteoporotic medication(18) and glucocorticoids(19) in all cohorts at baseline and during follow-up. Bone-altering medication comprised: bisphosphonates, calcitonin, teriparatide, proton pump inhibitors, selective estrogen receptor modulators, oral corticosteroids, thiazides, postmenopausal hormone therapy, contraceptives, androgens, anti-androgens, and fluorides. Similarly, we collected all available data on thyroid-altering medication: thyroxine, anti-thyroid drugs, lithium, and amiodarone.

Annualized Percentage Change in Bone Mineral Density (%ΔBMD)

Our primary outcome was the annualized percentage change between baseline and the last available follow-up measurements (%ΔBMD) at the femoral neck, total hip, and lumbar spine, in order to standardize BMD measurements across different cohorts, devices and follow-up durations, as in former study-level meta-analyses.(20, 21)

All BMD measurements were obtained from gold-standard dual x-ray absorptiometry (DXA, Appendix Table 1). The rationale for total hip, femoral neck, and lumbar spine as reference body sites was their high relevance to the risk assessment of major osteoporotic fractures.(22) To increase the accuracy and reproducibility for each body site, all cohorts implemented a strict quality control with cross-calibration using standardized phantoms to avoid inter-device variability and longitudinal shifts and drifts (Appendix Table 2).

In a previous publication, we observed an increased risk of hip fractures in participants with SHyper.(7) In the current work, we also examined whether this could be explained by the mediating effect of increased bone loss in this region. For this secondary analysis, every cohort provided us with both data on incident fractures and %ΔBMD. The definitions of fracture categories are detailed elsewhere.(7)

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Data Analysis

Following recommendations for IPD analyses (23, 24) and previous studies,(7, 14) we used a random-effects two-step approach, first analyzing associations between thyroid status and %ΔBMD for each cohort using linear multivariable regression models controlling for age, sex, body mass index (BMI),(25) diabetes mellitus,(25) smoking,(26) and menopausal status.(27) Data were complete for age and sex, with rare missing data for BMI (0·2%), smoking (0·3%), menopausal status (0·3%), and diabetes mellitus (<0·01%). This approach yielded adjusted differences in %ΔBMD between euthyroid individuals and those with SHyper or SHypo, and respective standard errors. In a second step, we calculated pooled estimates with 95%CI using inverse-variance random-effects models,(28) and assessed the heterogeneity across cohorts by means of I^2 statistic.(29). Additional information is detailed in the Appendix.

Results

Out of 1,558 articles identified in our literature search and through contact with experts, six cohort studies met all inclusion criteria (Appendix Figure 1).(10) Two other cohorts were potentially eligible, but not included because of different BMD measurement techniques and devices.(30, 31) The final sample for our primary outcome comprised 5,458 individuals (median age 72 years, 49·1% female participants) with a median follow-up of 6·7 years and total observation of 36,569 patient-years (Table 1). 4,723 (86·5%) participants were euthyroid, 451 (8·3%) had SHypo, and 284 (5·2%) had SHyper, including 230 (4·2%) with low but not suppressed TSH (0·10-0·44 mIU/l) and 54 (1·0%) with suppressed TSH (<0·10mIU/l). According to the modified Newcastle-Ottawa Quality Assessment Scale,(13) study quality was good to excellent with three studies achieving the full score of seven,(32-34) and three studies with six points (Appendix Table 2).(10, 35, 36)

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In euthyroid individuals, femoral neck BMD decreased 0·59% per year (95%CI:0·54, 0·63), total hip BMD decreased 0·55% per year (95%CI:0·49, 0·61), while spine BMD increased 0·32% per year (95%CI:-0·21, 0·84) in unadjusted models. In multivariable regression models, SHyper was associated with an increased bone loss at the femoral neck compared to euthyroidism: %ΔBMD=-0·18 (95%CI:-0·34, -0·02; I^2=0·0%, Appendix Figure 2), with a non-statistically significant pattern for total hip: %ΔBMD=-0·14 (95%CI:-0·38, 0·10, I^2=52·7%), but not for lumbar spine: %ΔBMD=0·03 (95%CI:-0·30, 0·36; I^2=24·8%) (Table 2). Among participants with SHyper and TSH <0·10 mUI/l, bone loss notably increased at the femoral neck [%ΔBMD=-0·59 (95%CI:-0·99,-0·19, I^2=0·0%)], with a similar pattern at the total hip [%ΔBMD=-0·46 (95%CI:-1·05,0·13, I^2=59·5%)] compared to euthyroidism. In contrast, SHypo was not associated with increased bone loss at any body site (Appendix Table 3). An analysis stratifying for cohort-specific fT4 quartiles resulted in a significantly increased hip bone loss in the highest vs. lowest fT4 quartile for both femoral neck %ΔBMD=-0·18 (95%CI:-0·29, -0·06, p<0·01) and total hip %ΔBMD=-0·20 (95%CI:-0·27, -0·12, p=0·02, Figure 1). In SHyper, bone loss was significantly increased for both men and women at the femoral neck (%ΔBMD=-0·33 [95%CI:-0·66, -0·01] vs. %ΔBMD=-0·14 [95%CI:-0·24, -0·05]) compared to euthyroidism, however without effect modification by gender (p for interaction 0·58), but not total hip (%ΔBMD=-0·38 [95%CI:-0·80, 0·03] vs. %ΔBMD=-0·05 [95%CI:-0·25, 0·14], p for interaction=0·43). There was a pattern for a larger bone decrease at the femoral neck among participants with SHyper ≥75 vs. < 75 years (%ΔBMD=-0·34 [95%CI:-0·52, -0·16] vs. %ΔBMD=-0·13 [95%CI:-0·22, -0·04], p for interaction=0·09), but not at the total hip (%ΔBMD=-0·28 [95%CI:-0·69, 0·12] vs. %ΔBMD=-0·15 [95%CI:-0·33, 0·04], p for interaction=0·77).

Most sensitivity analyses yielded similar results (Table 2), whereas exclusion of both thyroid- and bone-altering drug users at any time showed a greater bone loss in SHyper at the femoral

neck and a comparable pattern for total hip, without significant changes for lumbar spine. When excluding studies with >20% missing follow-up BMD, bone loss was significantly increased in SHyper at both hip measurement sites.

The adjusted HR for fractures associated with SHyper was 1·47 (95%CI:0·74, 2·91; p=0·27) for hip, 1·19 (95%CI:0·69, 2·03; p=0·53) for any, and 0·95 (95%CI:0·58, 1·57; p=0·85) for non-spine fractures. Compared to our previous publication,(7) confidence intervals were larger due to the smaller number of individuals with both fracture assessment and serial BMD scans (N=5,458 vs. N=70,298). Additional adjustment for baseline BMD and %ΔBMD in the total hip region yielded lower risk estimates, particularly for hip fractures (HR=1·28; 95%CI:0·64, 2·54; p=0·49). Additionally, there was no significant effect modification by thyroid status (SHyper vs. euthyroidism) in the association between %ΔBMD in the hip region and the risk for hip, non-spine and any fractures (Appendix Table 4).

Discussion

In our IPD analysis of 5,458 individuals from six population-based prospective cohorts, SHyper was associated with a moderately increased annualized bone loss at the femoral neck with a similar, non-significant trend for total hip, but not for lumbar spine, which may be influenced by the development of degenerative arthritis and vascular calcification. Bone loss at the femoral neck and total hip was largest among individuals with TSH levels <0·10 mUI/l showing approximately a double to 3-fold annualized rate of hip bone loss. Moreover, participants in the highest fT4 quartile had a more pronounced hip bone loss than participants in the lowest fT4 quartile. Conversely, SHypo was not associated with increased bone loss compared to euthyroid controls.

Bone loss at the femoral neck and, to a lesser extent, at total hip, was even greater after excluding individuals on bone metabolism and/or thyroid function-altering medication at any time. These results suggest increased hip bone loss especially in endogenous forms of

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SHyper, and are compatible with a recent study-level meta-analysis with 78% higher fracture risk in endogenous and 25% higher in exogenous forms of SHyper vs euthyroidism. (37) A cross-sectional study among 88 postmenopausal women reported significantly lower hip and lumbar spine BMD levels in endogenous, but not exogenous SHyper.(38) Longer exposure to decreased TSH levels in endogenous SHyper could be an explanation,(37, 39) as exogenous SHyper is usually quickly corrected with regular TSH monitoring.

Although there was no evidence of interaction by age or sex on the association between SHyper and hip bone loss, point estimates for femoral neck/total hip %ΔBMD in SHyper were lower in men than in women. These results are compatible with our previous publication showing a higher HR for hip fractures in men than in women with SHyper compared to euthyroid controls ([HR=1·92, 95%CI:1·26, 2·94] vs. [HR=1·29, 95%CI:1·08, 1·55], p for interaction 0·09).(7)

Our study found a potential mediating effect of hip bone loss in the association between SHyper and increased risk for hip fractures, as shown by the decreased HRs after additional adjustment for %ΔBMD and baseline BMD at the total hip. However, confidence intervals were large and the association was not statistically significant , as power was limited by the relatively low number of hip fractures (265 in the present analysis compared to 2,975 in our previous article).(7) Additionally, we found no clear interaction of thyroid status (SHyper vs euthyroidism) in the association between %ΔBMD in the hip region and fracture risk. Therefore, there may be additional mediators such as bone turnover and neuromuscular function in the association between SHyper and fracture risk. SHyper has been associated with reduced muscle strength,(40) increased frailty,(41) and an increased cardiovascular morbidity(15) in previous prospective cohorts, which all may result in an increased risk for falls and subsequent low-traumatic fractures.

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Our study has the following strengths. It is the first analysis on the association between SCTD and bone loss including a large proportion of IPD from six prospective population-based cohort studies from five different countries with a balanced gender distribution. Compared to study-level meta-analyses, an IPD analysis increases the power and accuracy of aggregated evidence by providing highly standardized and confounder-adjusted results from different cohort studies and reliable data on subgroups without ecological fallacy.(23) Although causality and the role of a drug intervention cannot be established in a cohort study, these data represent the best available evidence, as there is no published or ongoing randomized controlled trial on this topic to our knowledge. We could exclude individuals on thyroid- and bone-altering medication at any time point in our main and sensitivity analyses reducing the possibility of treatment bias.

However, our study has some limitations. First, we could not assess the association between persistent SCTD and bone loss, as serial thyroid hormone measurements were obtained only in one cohort. SHyper has an annual spontaneous progression rate of only 1-2%,(16) and SHypo of 3-4%(6) to overt thyroid disease. In a sensitivity analysis, we accounted for this issue excluding both bone- and thyroid-altering drug users at any time, which found an even faster bone loss at the femoral neck in SHyper. Second, the etiology of SHyper was not systematically assessed which precluded further subgroup analyses. Third, available information on drug treatment varied somewhat in detail and time span. However, missingness for thyroid- or bone-altering drugs at baseline was negligible (thyroid replacement therapy [0·75%], anti-osteoporotic agents [1·06%], oral corticosteroids [0·76%]). Fourth, our study population was older than the general population, which may reduce the generalizability of our results to younger individuals with SHyper. Fifth, only the OPUS(36) offered information on triiodothyronine (T3) levels, which made a uniform exclusion of participants with abnormal T3 values impossible. Thus, some individuals suffering from T3-

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toxicosis or non-thyroidal illness may have been included in the subgroup of SHyper. Finally, although we observed a potential mediating effect of total hip %ΔBMD in the association between SHyper and hip fractures, this secondary analysis was subject to limited power shown by large confidence intervals.

Conclusion

Hip bone loss was increased in individuals with SHyper, especially in those with TSH <0·10mIU/l, high-normal fT4 levels, and SHyper of potentially endogenous etiology, compared to euthyroidism. These results suggest that individuals with SHyper may be exposed to a greater osteoporosis risk due to accelerated hip bone loss. Although bone loss may not solely be responsible for the increased fracture risk, SHyper would represent a treatable risk factor.

Acknowledgements

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Contribution

Conflict of interest

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Table 1: Baseline Characteristics of Included Cohort Studies

	General				Follow-up for Bone Mineral Density			Thyroid Status		Thyroid Drugs *		Anti-osteoporotic Drugs [†]
Cohort	Sample characteristics	N	Age (median,IQR) years	Female (%)	Baseline, years	Median (IQR), years	Person-years	SHyper (%)	SHypo (%)	Baseline	Follow-up [‡]	Follow-up [‡]
Cardiovascular Health Study(35)	CDA aged ≥65y with Medicare eligibility in 2 US communities [§]	425	75·0 (73·0-78·0)	229 (53·9%)	1994-1995	4·0 (4·0-4·0)	1,700	17 (4·0%)	42 (9·9%)	50 (11·8%)	63 (14·8%)	29 (6·8%)
Health ABC Study(32) [‖]	CDA aged 70-79y with Medicare eligibility in 2 US communities	1,772	74·0 (72·0-77·0)	709 (40·0%)	1997-1998	8·8 (4·9-9·0)	15,594	49 (2·8%)	228 (12·9%)	142 (8·0%)	227 (12·8%)	153 (8·6%)
Osteoporotic Fractures in Men (MrOS) Study(10)	CDMs aged ≥ 65y in 6 US clinical centers	910	72·0 (68·0-76·0)	0 (0%)	2000-2002	6·7 (6·5-6·9)	6,097	11 (1·2%)	77 (8·5%)	51 (5·6%)	97 (10·7%)	64 (7·0%)
Osteoporosis and Ultrasound Study (OPUS)(36)	Women aged 20-80y, Germany, France, UK	665	63·6 (39·5-70·4)	665 (100%)	1999-2001	6·0 (5·8-6·2)	3,990	102 (15·3%)	4 (0·6%)	0 (0·0%)	31 (4·7%)	29 (6·8%)
Rotterdam Study(34)	Adults aged 55y+, Netherlands	1,531	68·1 (62·6-73·9)	924 (60·4%)	1990-1993	7·0 (2·9-11·1)	10,717	101 (6·6%)	84 (5·5%)	36 (2·4%)	36 (2·4%)	22 (1·4%)
Sheffield Study(33)	Women aged 50-85y, Sheffield, UK	155	63·5 (57·7-68·8)	155 (100%)	1990-1991	10·0 (5·1-10·0)	1,550	4 (2·6%)	16 (10·3%)	0 (0·0%)	9 (5·8%)	23 (14·8%)
Overall	6 cohorts	5,458	72 (67·0-76·0)	2,682 (49·1%)	1990-2001	6·7 (4·8-8·9)	36,569	284 (5·2%)	451 (8·3%)	279 (5·1%)	463 (8·5%)	328 (6·0%)

Footnote:

Values given in absolute numbers and percentages for participants with serial dual-x-ray-absorptiometry (DXA) scans. For medication, percentage is related either to total number at baseline or follow-up, as appropriate. Abbreviations: BMD: bone mineral density at any site of interest (femoral neck, total hip, lumbar spine). CA: California; CDA: community-dwelling adults; CDM: community-dwelling men; IQR: interquartile range; MD: Maryland; NC: North Carolina; PA: Pennsylvania; UK: United Kingdom; US: United States; y: years.

Baseline characteristics for main analysis after exclusion of participants with one, or a combination of, bone-altering medication at baseline: hormone replacement therapy (n=878), anti-osteoporotic treatment (n=226, including bisphosphonates, calcitonin, teriparatide, selective estrogen receptor modulators, fluoride), proton pump inhibitors (n=177), oral corticosteroids (n=78), contraceptives (n=28), androgens (n=8), anti-androgens (n=2),

* Thyroid-altering medication includes thyroid hormone replacement therapy and anti-thyroid drugs. OPUS and Sheffield Study did not record anti-thyroid drugs. Additional thyroid-altering drugs vary across studies and are considered in our main analysis

† Anti-osteoporotic medication includes: bisphosphonates, calcitonin parathyroid hormone, selective estrogen receptor modulators, fluoride substitution. Additional bone-altering agents vary across studies and are considered in our main analysis.

‡ Different follow-up durations for BMD across studies and participants, therefore individual information provided for each patient.

§ Baseline and follow-up DXA scans from the study site in Pittsburgh, PA

‖ Thyroid status measured one year after 1st BMD measurement

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Table 2: Sensitivity Analyses for the Multivariable-Adjusted* Association between Subclinical Hyperthyroidism and Annualized Change in Bone Mineral Density

	N SHyper/Euthyroidism	%ΔBMD	95%CI	I^2	p
Femoral Neck					
Main analysis: **Exclusion of bone drug users at baseline**	**283/4700**	-0·18	-0·34; -0·02	0·0%	0·44
and no history of osteoporosis, and/or previous, and/or incident fractures	222/3517	-0·23	-0·45; <-0·01	23·2%	0·26
Exclusion of bone drug users[†] at any time	234/3559	-0·18	-0·36; <-0·01	0·0%	0·48
Exclusion of both thyroid[‡]- and bone-influencing drug users at any time	184/3348	-0·36	-0·71; <-0·01	45·9%	0·10
Exclusion of cohorts with >20% missing follow-up BMD [§]	154/2968	-0·36	-0·63; -0·09	0·0%	0·56
Inclusion of participants with TSH<0.10mIU/l only	54/4700	-0·59	-0·99; -0·19	0·0%	0·44
Total Hip					
Main analysis: **Exclusion of bone drug users at baseline**	**232/4122**	-0·14	-0·38; 0·10	52·7%	0·06
and no history of osteoporosis, and/or previous, and/or incident fractures	181/3013	-0·17	-0·53; 0·19	74·5%	<0·01
Exclusion of bone drug users[†] at any time	184/3037	-0·16	-0·47; 0·15	60·8%	0·03
Exclusion of both thyroid[‡]- and bone-influencing drug users at any time	141/2844	-0·40	-0·96; 0·16	81·9%	<0·01
Exclusion of cohorts with >20% missing follow-up BMD [§]	103/2389	-0·38	-0·65; -0·10	15·8%	0·31
Inclusion of participants with TSH<0.10mIU/l only	42/4122	-0·46	-1·05; 0·13	59·5%	0·04
Lumbar Spine					
Main analysis: **Exclusion of bone drug users at baseline**	**163/2974**	0·03	-0·30; 0·36	24.8%	0·26
and no history of osteoporosis, and/or previous, and/or incident fractures	121/1985	-0·06	-0·42; 0·29	19·5%	0·29
Exclusion of bone drug users[†] at any time	128/2069	0·33	-0·35; 1·00	64·6%	0·04
Exclusion of both thyroid[‡]- and bone-influencing drug users at any time	101/1930	0·39	-0·47; 1·25	64·7%	0·04
Exclusion of cohorts with >20% missing follow-up BMD [§]	53/1619	0·36	-0·55; 1·28	62·5%	0·10
Inclusion of participants with TSH<0.10mIU/l only	23/2974	0·44	-1·12; 0·24	0·0%	0·52

Footnote: Abbreviations: %ΔBMD: annualized percentage change in bone mineral density compared to euthyroid individuals, I^2: I^2 statistics, 95%CI: 95% confidence intervals; N: number of participants; p = p for heterogeneity, SHyper: subclinical hyperthyroidism.

Multivariable adjustment for age, sex, bone mass index, smoking and menopausal status, history of diabetes. Values presented as mean difference in annualized percentage change in BMD, as compared to euthyroid controls.

Bone-altering drug users with intake of either bisphosphonates, calcitonin, teriparatide, selective estrogen receptor modulators, oral corticosteroids, thiazide diuretics, androgens, anti-androgens, hormone replacement therapy or proton pump inhibitors.

Thyroid-altering drug users with intake of either thyroxine, antithyroid drugs, amiodarone, or lithium.

Exclusion of the Cardiovascular Health Study (35), Osteoporotic Fractures in Men (MrOS) Study(42) and Osteoporosis and Ultrasound Study (OPUS)(36) for the sensitivity analysis of %ΔBMD at the femoral neck and total hip. Additionally, no data available for %ΔBMD at the lumbar spine in Rotterdam Study.(34)