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Association between thyroid function and osteopenia or osteoporosis: a cross-sectional study in China

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Thyroid dysfunction is associated with bone health, but the relationship with osteopenia remains unclear. This study aimed to investigate the association between thyroid function and osteopenia/osteoporosis across different age groups. The study included 4508 men and 1438 women who underwent health check-ups between January 2021 and December 2023. Bone mineral density (BMD) was measured using dual energy X-ray absorptiometry. Logistic regression analysis was employed to evaluate the association between thyroid function and the risk of osteopenia/osteoporosis. The results showed that in postmenopausal women, both hyperthyroidism and age increased the risk of osteopenia and osteoporosis, while body mass index (BMI) was negatively correlated with both conditions. In men over 50, hyperthyroidism and age were also linked to a higher risk of osteoporosis. Among postmenopausal women, higher thyroid-stimulating hormone (TSH) levels were negatively associated with osteopenia risk. In men aged 50 and above, free thyroxine (fT4) levels were inversely related to osteopenia and osteoporosis risk. In men under 50, fT4 levels were negatively linked to the risk of low bone mass. These findings suggest that TSH and fT4 levels may influence bone health, with these effects varying by age and sex. Further studies are needed to confirm these findings and explore potential mechanisms.

Keywords Osteopenia, Osteoporosis, Hyperthyroidism, Hypothyroidism, Thyroid-stimulating hormone (TSH), Free thyroxine (FT4)

Osteoporosis, characterized by reduced bone density and structural deterioration throughout the skeletal system, predisposes individuals to fragility fractures[1]. Osteopenia, on the other hand, denotes an intermediate phase in bone health, situated between normal bone mineral density (BMD) and osteoporosis, where bone density is below optimal levels but not as severely compromised as in osteoporosis[2]. If left untreated, osteopenia often progresses to osteoporosis[3]. The global prevalence of osteoporosis among women is estimated at 23.1%[4]. In the United States, approximately 10 million individuals aged 50 or older have been diagnosed with osteoporosis, while an additional 34 million are at risk[5]. Osteoporosis results in a substantial economic burden, with an estimated annual cost of £4.7 billion in the UK[6].

Thyroid dysfunction is among the most prevalent endocrine disorders[7]. Several studies have demonstrated a correlation between thyroid dysfunction and skeletal outcomes[8]. Hyperthyroidism accelerates bone resorption relative to bone formation, leading to decreased bone density and an elevated risk of fractures[9]. Conversely, there is insufficient evidence regarding the effects of hypothyroidism on bone health[10]. Research on the relationship between subclinical thyroid dysfunction and bone-related outcomes has yielded conflicting results[11]. For instance, Lee et al. observed a reduction in BMD at the femoral neck in women with subclinical hyperthyroidism but found no such changes in the lumbar spine. They also did not identify significant differences in serum

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levels of bone turnover markers[12]. Most studies focusing on premenopausal women have not shown a strong association between subclinical hyperthyroidism and low BMD or increased fracture risk[13]. However, limited research has been conducted on the relationship between subclinical hyperthyroidism and bone health in men, with most prior studies primarily addressing the risk of hip fractures[8]. A comprehensive review of cohort studies found no conclusive evidence supporting a definite link between subclinical hypothyroidism and BMD[14]. Some studies suggest that TSH may have a direct protective effect on bone, independent of thyroid hormone levels[15]. Most previous research has primarily focused on parameters such as bone density, osteoporosis, and fractures, with limited exploration specifically into bone loss. Furthermore, most studies have concentrated on only one or two categories of thyroid dysfunction[16]. Additionally, fewer studies have examined how abnormal thyroid function affects bone health in men under 50 and in premenopausal women.

In this study, we aimed to investigate the relationship between thyroid function and osteopenia and osteoporosis in both pre- and postmenopausal women as well as men. Additionally, we sought to clarify the associations between thyroid hormone concentrations and osteopenia or osteoporosis. Given the interdependence of skeletal responses to thyroid hormones, conducting studies on healthy euthyroid individuals may not be fully applicable, as the hypothalamic-pituitary-thyroid (HPT) axis regulates the balance between fT4, triiodothyronine (fT3), and TSH at a physiological level, maintaining stable thyroid function. Therefore, we included a diverse range of populations in our analysis[17].

Materials and methods

Study population and design

There was a cross-sectional study involving all participants who underwent health check-ups at Shandong Provincial Hospital Heze Branch in Shandong province, China, from January 2021 to December 2023. During the consultation, we collected data on participants' medical history, medications, family history, and surgical history to mitigate potential confounding factors. The study's exclusion criteria were as follows: participants with a history of cancer, diabetes mellitus, chronic kidney disease, pituitary disease, or any other condition affecting bone metabolism; those using medications that impact bone health, such as calcium or steroids; individuals using thyroid hormones, and individuals with incomplete information. After exclusions, a total of 5946 participants were included in this study. During the physical examination, body height (BH), body weight (BW), and blood pressure (BP) were measured. BMI was determined by dividing BW by the square of BH (kg/m^2). Fasting blood samples were collected, and an automated biochemical analyzer (Roche Cobas 8000, Japan) was used to assess the levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL-C), and high-density lipoprotein (HDL-C) on the same day. TSH, fT4, and fT3 were examined using the fully automated chemiluminescence immunometric analyzer on the Cobas 8000 e601 (Roche Diagnostics). TSH has an inter-assay CV of 3.2% and an intra-assay CV of 2.1%, while fT4 has an inter-assay CV of 4.5% and an intra-assay CV of 3.8%. Blood pressure was assessed while seated following 10 min of rest, employing an electronic sphygmomanometer (U703; Omron, Dalian, China). The study received approval from the Ethics Committee of Shandong Provincial Hospital Heze Branch (2024-KY001-079), and followed the principles outlined in the Declaration of Helsinki. All participants provided written informed consent.

Diagnostic criteria.

In our institution, the reference ranges were: TSH 0.35–5.10 μIU/ml, fT4 0.87–1.85 ng/dl, fT3 1.8–4.2 pg/ml.

Overt hyperthyroidism: TSH < 0.35 uIU/mL; fT4 > 1.85 ng/dl or fT3 > 4.2 pg/mL.

Subclinical hyperthyroidism: TSH < 0.35 uIU/mL; fT4 within the normal range (0.87–1.85 ng/dl).

Overt hypothyroidism: TSH > 5.1 uIU/mL; fT4 < 0.87 ng/dl.

Subclinical hypothyroidism: TSH > 5.1 uIU/mL; fT4 within the normal range.

Euthyroidism: TSH 0.35–5.1 uIU/mL; fT4 0.87–1.85 ng/dl.

The BMD of the distal radius was assessed using dual-energy X-ray absorptiometry (DCS-600EXV, Japan). Following the criteria outlined by the World Health Organization[18], postmenopausal women and men aged over 50 years were categorized into three groups: normal (T-score of − 1.0 or higher), osteopenia (T-score ranging from − 2.5 to − 1.0), and osteoporosis (T-score of ≤ − 2.5). For both premenopausal women and men under 50 years of age, the Z-score was calculated from the BMD data. A Z-value of − 2.0 or below signifies bone density levels that are considered beneath the anticipated range for an individual's age group or low bone mass[19].

Statistical analysis

The data were analyzed using SPSS 25.0 statistical software. For variables that exhibited a normal distribution, they are displayed as mean ± standard deviation (SD), while data with a skewed distribution is represented by the median (interquartile range) [Md (P25, P75)]. Quantitative variables are presented with counts and relative proportions. Rate comparisons were performed utilizing both the Chi-square test and Fisher's exact tests. For normally distributed data, comparisons among multiple groups were conducted using one-way analysis of variance (ANOVA). The Kruskal–Wallis H test was applied to assess variations among various groups in the case of non-normally distributed quantitative data. Post hoc pairwise comparisons between groups were adjusted utilizing the Bonferroni correction method to mitigate the risk of inflated type I error rates. A logistic regression analyses were employed to evaluate the associations between thyroid dysfunction and osteopenia, as well as osteoporosis. The results were presented in the form of odds ratios (ORs) and 95% confidence intervals (CIs). Statistical significance was defined as $P < 0.05$.

Results

Characteristics of the study population

A total of 5946 (4508 men and 1438 women) individuals over 18 years old were included in our study. The participants were categorized into five groups according to the level of TSH and fT4 (euthyroid, hyperthyroidism, subclinical hyperthyroidism, hypothyroidism, subclinical hypothyroidism). Table 1 displays the fundamental features of subjects within each group. The frequencies of hyperthyroidism, subclinical hyperthyroidism, hypothyroidism, and subclinical hypothyroidism were 1.14%, 1.12%, 0.8% and 8.19%, respectively. The median age of the subclinical hypothyroidism group was 57 (50, 63), significantly higher than that of the euthyroid group, 54 (48, 58). The prevalence of hyperthyroidism, hypothyroidism, and subclinical hypothyroidism among females is notably elevated compared to the euthyroid group (48.5%, 48.9%, 32.9%, and 22.7%, respectively; $P < 0.05$). Individuals in the hyperthyroidism group have higher levels of fT3 and fT4 than other groups. Meanwhile, in the subclinical hyperthyroidism group, fT4 levels were higher than in the hypothyroidism group, the subclinical hypothyroidism group, and the euthyroid group. In both the hypothyroidism and subclinical hypothyroidism cohorts, TSH exhibited a significantly higher level in contrast to the other three groups. Besides, the incidence of osteoporosis is notably elevated in the hyperthyroidism group as opposed to the euthyroid group (35.3% vs. 17.4%, $P < 0.05$). However, there were no significant differences among groups in BMI, TC, TG, LDL-C, HDL-C, and the prevalence of osteopenia.

Thyroid dysfunction and osteopenia/osteoporosis in postmenopausal women and men older than 50 years

Overall, 959 postmenopausal women and 3342 men older than 50 were enrolled in the study. The women had a mean age of 59.6 ± 8.8 years. The average age of men over 50 was 58.3 ± 7.4 years. Multivariable regression analysis revealed that both hyperthyroidism and age exhibited a positive association with the risk of osteopenia, as well as osteoporosis in postmenopausal women. The ORs for hyperthyroidism concerning osteopenia and osteoporosis were 5.00 and 5.47, respectively. Conversely, BMI was negatively correlated with osteopenia and osteoporosis. However, no association was found between subclinical hyperthyroidism, hypothyroidism, subclinical hypothyroidism, and the risk of osteopenia or osteoporosis in postmenopausal women (Table 2). For men aged over 50, the multivariate logistic regression analysis is presented in Table 3. Hyperthyroidism (OR 10.12, $P = 0.002$) and age (OR 1.05, $P < 0.001$) were significantly linked to the risk of osteoporosis. Otherwise, subclinical hyperthyroidism, hypothyroidism, and subclinical hypothyroidism did not have significant associations with osteoporosis. Meanwhile, no significant correlations were identified between thyroid dysfunction (including hyperthyroidism, subclinical hyperthyroidism, hypothyroidism, subclinical hypothyroidism), age, and BMI with osteopenia.

TSH, FT4, FT3, and osteopenia/osteoporosis in postmenopausal women and men older than 50 years

The average age of postmenopausal women is 59.6 ± 8.8 years, while the average age of men over 50 is 58.3 ± 7.4 years. Thyroid parameters were segmented into quartiles for assessing the associations. Among postmenopausal women, only those in the fourth quartile of TSH concentration exhibited a negative association with the risk of osteopenia compared to those in the first quartile (OR 0.55, $P = 0.009$) after accounting for age and BMI. No significant associations were observed between the risk of osteopenia and TSH concentrations in quartiles 2 to 3, or with fT4 and fT3 concentrations in quartiles 2 to 4. Furthermore, the risk of osteoporosis was not linked to the concentrations of TSH, fT4, and fT3 within quartiles 2–4. The results of multivariable logistic regression analyses are presented in Table 4. For males aged 50 years and above, the fT4 quartiles were adversely associated with osteopenia and osteoporosis in a multivariable regression analysis adjusted for age and BMI

	Euthyroid (n = 5277)	Hyperthyroidis (n = 68)	Subclinical hyperthyroidis (n = 67)	Hypothyroidism (n = 47)	Subclinical hypothyroidism (n = 487)
Age	54 (48, 58)	54 (43, 61)	55 (49, 58)	56 (52, 60)	57 (50, 63)a
Women (%)	1198 (22.7)	33 (48.5)a	24 (35.8)	23 (48.9)a	160 (32.9)a
BMI	25.4 ± 3.3	24.4 ± 2.7	25.2 ± 3.3	25.3 ± 2.5	24.8 ± 3.2
TSH	2.27 (1.70, 3.09)	0.035 (0.01, 0.13)[a]	0.06 (0.03, 0.23)[a]	6.93 (5.65, 20.81)[a]	6.06 (5.47, 7.37)[a]
FT3 (pg/ml)	3.09 (2.86, 3.36)	5.41 (4.46, 7.15)a	3.12 (2.85, 3.52)	2.61 (2.48, 2.89)[a]	3.02 (2.76, 3.32)[a]
FT4 (ng/dl)	1.24 (1.08, 1.41)	18.75 (5.46, 22.98)[a]	1.50 (1.27, 1.64)[a]	0.77 (0.71, 0.83)[a]	1.18 (1.03, 1.36)[a]
TC	4.61 (4.01, 5.28)	4.20 (3.68, 4.93)	4.55 (3.96, 5.26)	4.73 (3.91, 5.43)	4.77 (4.05, 5.43)
TG	1.37 (0.96, 2.03)	1.16 (0.90, 1.64)	1.42 (0.93, 1.82)	1.40 (1.13, 1.93)	1.41 (1.01, 2.03)
LDL	2.79 (2.26, 3.36)	2.51 (2.02, 3.12)	2.78 (2.30, 3.25)	2.90 (2.22, 3.38)	2.87 (2.26, 3.46)
HDL	1.16 (0.98, 1.39)	1.18 (0.96, 1.41)	1.11 (0.92, 1.40)	1.13 (0.98, 1.37)	1.24 (1.07, 1.57)
Osteopenia	2162 (40.9)	20 (29.4)	27 (40.3)	19 (40.4)	184 (37.8%)
Osteoporosis	916 (17.4)	24 (35.3)[a]	17 (25.4)	13 (27.7)	106 (21.8)

Table 1. Characteristics of the study population. BMI, body mass index; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. [a]Statistically different from euthyroid group ($P < 0.05$).

		be	P	OR (95% CI)
Osteopenia	Age	0.080	< 0.001*	1.08 (1.05, 1.11)
	BMI	− 0.063	0.027*	0.94 (0.89, 0.99)
	Hyperthyroidism	1.608	0.017*	5.00 (1.33, 18.72)
	Subclinical hyperthyroidism	0.531	0.378	1.70 (0.52, 5.54)
	Hypothyroidism	0.767	0.189	2.15 (0.69, 6.77)
	Subclinical hypothyroidism	− 0.401	0.106	0.67 (0.41, 1.09)
Osteoporosis	Age	0.19	< 0.001*	1.21 (1.18, 1.24)
	BMI	− 0.077	0.015*	0.93 (0.87, 0.99)
	Hyperthyroidis	1.699	0.021*	5.47 (1.30, 23.05)
	Subclinical hyperthyroidism	0.753	0.244	2.12 (0.60, 7.53)
	Hypothyroidism	0.193	0.801	1.21 (0.27, 5.42)
	Subclinical hypothyroidism	− 0.362	0.185	0.70 (0.41, 1.19)

Table 2. Multiple logistic regression of postmenopausal women. BMI, body mass index; CI, confidence interval; OR, Odds ratio. *$P < 0.05$.

		be	*P*	OR (95% CI)
Osteopenia	Age	− 0.006	0.333	0.99 (0.98, 1.01)
	BMI	− 0.015	0.236	0.99 (0.96, 1.01)
	Hyperthyroidism	1.076	0.174	2.93 (0.62, 13.85)
	Subclinical hyperthyroidism	− 0.124	0.773	0.88 (0.38, 2.05)
	Hypothyroidism	0.906	0.17	2.48 (0.68, 9.03)
	Subclinical hypothyroidism	0.032	0.833	1.03 (0.77, 1.39)
Osteoporosis	Age	0.047	< 0.001*	1.05 (1.18, 1.24)
	BMI	− 0.014	0.392	0.97 (0.96, 1.02)
	Hyperthyroidism	2.315	0.002*	10.12 (1.30, 23.05)
	Subclinical hyperthyroidism	0.511	0.264	1.67 (0.68, 4.08)
	Hypothyroidism	1.072	0.127	2.92 (0.74, 11.59)
	Subclinical hypothyroidism	− 0.036	0.845	0.97 (0.67, 1.38)

Table 3. Multiple logistic regression of men older than 50 years. BMI, body mass index; CI, confidence interval; OR, Odds ratio. *$P < 0.05$.

(all $P < 0.001$, except quartile 2 of fT4 for osteopenia $P = 0.005$). However, no associations were found between quartiles of TSH or fT3 and the risk of osteopenia or osteoporosis (Table 4).

TSH, FT4, FT3, and low bone mass in premenopausal women and men younger than 50

Table 5 displays the outcomes of binary logistic regression analysis investigating the association between thyroid function and low bone mass in premenopausal women and men younger than 50. The quartiles of TSH, fT4, and fT3 were not correlated with the risk of low bone mass for premenopausal women. However, quartile 2 of TSH concentration in men younger than 50 showed a weak negative correlation with the risk of low bone mass compared with quartile 1(OR 0.72, $P = 0.049$). FT4 quartiles were linked to a decreased risk of low bone mass compared to quartile 1(ORs for quartiles 2–4 were 0.62, 0.60, and 0.64, respectively). No associations were observed between quartiles of TSH (quartiles 3–4), fT4 (quartiles 2–4), fT3 (quartiles 2–4) concentration, and low bone mass risk in men under 50.

Discussion

Our study demonstrated that in postmenopausal women, hyperthyroidism and advanced age have a negative impact on osteopenia and osteoporosis, whereas BMI serves as a protective factor against both conditions. For men aged over 50, only hyperthyroidism and age can increase the risk of osteoporosis. Nonetheless, there are no significant associations between subclinical thyroid dysfunction, hypothyroidism, and risk of osteopenia or osteoporosis in the aforementioned two populations. To our knowledge, we enrolled more indicators of thyroid dysfunction (including euthyroid, hyperthyroidism, subclinical hyperthyroidism, hypothyroidism, and subclinical hypothyroidism) and thyroid hormones (TSH, fT4 and fT3). Furthermore, we conducted an analysis of premenopausal women and males below the age of 50. Our study can shed new light on the connection between thyroid dysfunction, thyroid hormones, and osteopenia, as well as osteoporosis across different age groups and genders.

Numerous studies have examined the correlation between hyperthyroidism, hypothyroidism, and the presence of osteopenia or osteoporosis. The majority of studies showed that the BMD of both women and men

		Postmenopausal women				Men older than 50 years			
	Quartile	Osteopenia	*P*	Osteoporosis	*P*	Osteopenia	*P*	Osteoporosis	*P*
TSH	1	1		1		1			
	2	0.78 (0.50, 1.21)	0.265	0.83 (0.50, 1.38)	0.473	0.89 (0.72, 1.11)	0.650	0.86 (0.65, 1.12)	0.395
	3	0.82 (0.53, 1.27)	0.366	0.68 (0.41, 1.14)	0.146	1.11 (0.89, 1.38)	0.356	1.08 (0.82, 1.41)	0.599
	4	0.55 (0.35, 0.86)	0.009*	0.64 (0.39, 1.06)	0.085	0.95 (0.77, 1.18)	0.304	0.89 (0.68, 1.17)	0.257
$P_{for\ trend}$			0.068		0.937		0.437		0.642
FT4	1	1		1		1		1	
	2	0.78 (0.51, 1.21)	0.269	0.65 (0.39, 1.09)	0.100	0.73 (0.58, 0.91)	0.005*	0.54 (0.41, 0.71)	< 0.001*
	3	1.34 (0.86, 2.08)	0.199	1.31 (0.80, 2.16)	0.287	0.66 (0.53, 0.83)	< 0.001*	0.56 (0.43, 0.73)	< 0.001*
	4	1.02 (0.66, 1.59)	0.917	0.91 (0.55, 1.50)	0.706	0.65 (0.52, 0.81)	< 0.001*	0.50 (0.38, 0.65)	< 0.001*
$P_{for\ trend}$			0.867		0.081		0.063		0.002*
FT3	1	1		1		1		1	
	2	0.83 (0.54, 1.29)	0.416	0.74 (0.44, 1.23)	0.240	1.06 (0.86, 1.33)	0.578	0.94 (0.72, 1.23)	0.653
	3	1.07 (0.69, 1.66)	0.762	1.15 (0.70, 1.91)	0.581	1.07 (0.86, 1.33)	0.553	0.93 (0.71, 1.23)	0.611
	4	1.11 (0.71, 1.75)	0.646	1.08 (0.65, 1.79)	0.765	1.20 (0.96, 1.50)	0.107	1.17 (0.89, 1.53)	0.254
$P_{for\ trend}$			0.579		0.736		0.076		0.413

Table 4. Association between thyroid indicators and osteopenia/osteoporosis in postmenopausal women and men older than 50 years. TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine. In Postmenopausal women, the cut-offs for the quartiles of TSH were 1.80 μIU/ml, 2.72 μIU/ml, and 4.04 μIU/ml; for fT4 1.06 ng/dl, 1.21 ng/dl, and 1.42 ng/dl; for fT3 2.67 pg/ml, 2.91 pg/ml, and 3.25 pg/ml. In men older than 50 years old, the cut-offs for the quartiles of TSH were 1.70 μIU/ml, 2.31 μIU/ml, and 3.31 μIU/ml; for fT4 1.07 ng/dl, 1.23 ng/dl, and 1.40 ng/dl, for fT3 2.90 pg/ml, 3.10 pg/ml, and 3.35 pg/ml; OR and 95% CI were calculated using logistic regression models and adjusted for age and BMI, $^*P < 0.05$.

was decreased in untreated patients with hyperthyroidism[20], especially in postmenopausal women[21,22]. Our findings align with those of prior research. In adults, overt hyperthyroidism accelerates the bone remodeling cycle by up to 50% and disrupts the balance between bone formation and resorption processes[23]. This imbalance can lead to lower BMD and a higher likelihood of experiencing fragility fracture[24]. Tuchendler et al. reported that hypothyroidism has no impact on BMD in premenopausal females[25]. Mohamed et al. demonstrated a decreased bone mass in men with hypothyroidism compared to the euthyroid group[26]. The men in their study were younger, with a lower average age of 51.66 ± 1.64 years than in our study (54.1 ± 10.2 years). In our investigation, we performed a multiple regression analysis, which did not unveil any notable association between hypothyroidism and either osteopenia or osteoporosis. Limited studies, including ours, suggested that subclinical hypothyroidism may not be a significant risk factor for hip fractures or influence BMD in both men and women[27,28]. The Cardiovascular Health Study, which examined community-dwelling individuals aged 65 and above, found neither subclinical hypothyroidism nor subclinical hyperthyroidism appears to be associated with changes in BMD or hip fracture risk[11]. However, conflicting reports have suggested an association between subclinical dysfunction and BMD. A study included 13 patients diagnosed with nodular goitre accompanied by subclinical hyperthyroidism reported that BMD was decreased (TSH range 0.76–3.9 uIU/mL)[29]. Early postmenopausal patients with endogenous subclinical hyperthyroidism exhibited a notable rise in bone turnover markers and a decline in lumbar BMD (TSH range 0.3–3.5 uIU/ml)[30]. Conversely, an increased BMD in the legs in patients with subclinical hypothyroidism was reported[31]. In our study, the average ages of postmenopausal women and men aged over 50 years enrolled in our study were older, at 59.64 ± 8.8 and 58.33 ± 7.4 years, respectively. In addition, we used a TSH reference range of 0.35–5.10 uIU/L, which was a higher range than used in the above studies.

In our study, after adjusting age and BMI, a high concentration of TSH was linked to a reduced risk of osteopenia in postmenopausal individuals. In addition, ft4 quartiles (2–4) were correlated with a reduced likelihood of developing osteopenia and osteoporosis in men aged over 50. However, we did not observe any associations between TSH, fT4, and fT3 quartiles and the risk of osteopenia in premenopausal women. For premenopausal women, our results were consistent with a similar study[32]. Previous research reported that postmenopausal women with elevated but still within normal range TSH levels had a higher BMD and a decreased risk of osteoporosis, and a decrease of 1 mU/l in TSH concentration raised the risk of osteoporosis by 20%[33]. Grimnes et al. discovered that in 993 postmenopausal women, those with TSH levels exceeding the 97.5th percentile exhibited higher femoral neck BMD than those with serum TSH levels ranging from the 2.5th to the 97.5th percentile[34]. In terms of both size and age, their sample population closely resembled ours, consisting of 993 subjects with an average age of 63 years[34]. Morris et al. documented that postmenopausal women whose TSH levels were within the higher normal range demonstrated a reduced risk of osteopenia and osteoporosis in comparison to individuals with TSH levels within the lower normal range, suggesting that TSH itself might contribute to bone preservation following menopause[15]. Hence, elevated TSH concentrations correlate with an increased likelihood of hypofunction. When categorizing individuals into quartiles based on TSH levels, we observed that those with serum TSH in Q4 group had a lower risk of osteopenia in postmenopausal women.

		Premenopausal women		Men younger than 50 years	
	Quartile	Low bone mass	*P*	Low bone mass	*P*
TSH	1	1		1	
	2	0.72 (0.36, 1.46)	0.359	0.72 (0.51, 1.00)	0.049*
	3	0.93 (0.47, 1.84)	0.834	0.87 (0.62, 1.21)	0.391
	4	0.71 (0.34, 1.46)	0.350	0.93 (0.67, 1.29)	0.664
$P_{for\ trend}$			0.559		0.794
FT4	1	1		1	
	2	1.15 (0.58, 2.30)	0.688	0.62 (0.45, 0.86)	0.004*
	3	1.13 (0.54, 2.34)	0.746	0.60 (0.43, 0.85)	0.003*
	4	1.12 (0.54, 2.31)	0.764	0.64 (0.45, 0.89)	0.008*
$P_{for\ trend}$			0.827		0.003*
FT3	1	1		1	
	2	0.68 (0.33, 1.38)	0.284	0.81 (0.58, 1.13)	0.209
	3	1.12 (0.57, 2.19)	0.748	0.93 (0.67, 1.30)	0.669
	4	0.72 (0.35, 1.48)	0.376	1.03 (0.74, 1.44)	0.870
$P_{for\ trend}$			0.708		0.407

Table 5. Association between thyroid indicators and low bone mas in premenopausal women and men under 50 years. TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine. In Premenopausal women, the cut-offs for the quartiles of TSH were 1.69 μIU/ml, 2.44 μIU/ml, and 3.45 μIU/ml; for fT4 1.060 ng/dl, 1.24 ng/dl, and 1.39 ng/dl; for fT3 2.67 pg/ml, 2.83 pg/ml, and 3.14 pg/ml. In men younger than 50 years old, the cut-offs for the quartiles of TSH were 1.71 μIU/ml, 2.29 μIU/ml, and 3.18 μIU/ml; for fT4 1.13 ng/dl, 1.30 ng/dl, and 1.48 ng/dl, for fT3 3.03 pg/ml, 3.26 pg/ml, and 3.54 pg/ml; OR and 95% CI were calculated using logistic regression models and adjusted for age and BMI, * $P < 0.05$.

Perhaps a subset of these individuals might have been in a hypothyroidism state. Research examining how TSH concentration relates to bone density in men is scarce, especially those under 50 years of age. A longitudinal population study studied 403 men with a mean age of 77.8 years, indicating no relation between hip BMD and serum TSH concentration[35]. In males 55 years or older, serum TSH levels falling below the 2.5th percentile were associated with notably lower distal forearm BMD compared to serum TSH levels within the normal range[34]. However, we only found TSH < 1.685 μIU/ml was a reduced risk of osteopenia in men younger than 50 years. Differences in the characteristics of the study populations and the sits of BMD may account for the disparity between our results and those of other studies. For example, the average age in the above two studies was older than in ours[34,35]. Furthermore, the sites of BMD used in the studies were different. Additionally, our population is younger and may have a higher BMI and fat mass, which affects bone density. Our previous studies have shown that BMI is associated with a low risk of bone loss and osteoporosis, although this relationship was not significant in men. Although our findings adjusted for age and BMI, it's important to note that fat mass cannot be avoided. Numerous studies have consistently shown that fat mass has a positive impact on bone health and serves as a protective factor against osteoporosis[36]. Currently, there are several possible mechanisms to explain the relationship between TSH and bone metabolism. Research has indicated that TSH negatively regulates the activity of both osteoblasts and osteoclasts. TSH primarily enhances osteoblast differentiation by activating protein kinase Cδ and upregulating noncanonical Wnt components[37]. Moreover, TSH suppresses the formation of osteoclasts by reducing the activation of NFkB and JNK/c-jun signaling pathways reaction to TNFα and RANK-L[38].

After adjusted age and BMI, we found that fT4 values were negatively associated with risk of osteopenia and osteoporosis in all men. A similar finding has been noted in the Indian population[39]. Conversely, in healthy euthyroid subjects, there has been a negative correlation between fT4 levels and bone mineral content[40]. Similarly, Murphy et al. documented a correlation between elevated concentrations of fT4 and fT3 and bone loss in the hip region among postmenopausal women[41]. However, Baqi et al. discovered no substantial correlation between fT4 levels and BMD in postmenopausal women[42]. Additionally, in premenopausal women, Baqi et al. noted the absence of any correlation between thyroid hormone levels and BMD[43].

This study holds significant value, as there have been few investigations into BMD in both pre- and post-menopausal women, as well as in men across all age groups. A key strength of this study is the inclusion of a large sample size, which enhances the reliability and clinical applicability of our findings. Additionally, the large cohort enables stratified analyses, revealing potential differences across subpopulations, which may help inform personalized bone density monitoring strategies. Although the large sample size may introduce confounders related to heterogeneity, we have mitigated these risks through the use of standardized protocols and statistical adjustments. However, it is important to note some limitations. We did not measure anti-thyroid antibodies, osteocalcin, vitamin D3, parathyroid hormone, and other related indicators in our study. Additionally, confounding factors such as alcohol and smoking consumption could not be fully controlled. In our study, most subjects visited our institution only once, so we defined subclinical hypothyroidism or hyperthyroidism on a single measurement of TSH, similar to other studies based on single TSH values[44–46]. In the future, follow-up

observations to explore the long-term effects of symptomatic subclinical thyroid dysfunction on osteopenia or osteoporosis were needed.

Conclusion

We found associations between hyperthyroidism and osteopenia and osteoporosis in postmenopausal women, and osteoporosis in men over the age of 50. For postmenopausal women, our results also suggested that TSH concentration was negatively associated with osteopenia. In men aged 50 and above, fT4 levels were inversely related to osteopenia and osteoporosis risk. In men under 50, ft4 levels were negatively linked to the risk of low bone mass. Our research suggests that maintaining elevated levels of TSH may contribute to preserving BMD after menopause. Conversely, in men, higher levels of fT4 and lower TSH may be beneficial for mitigating bone loss.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Author contributions

L.M. conceived and designed the project and contributed to acquisition of the data. L.Zh. performed analyses and wrote the manuscript. Ch.M. performed data analysis. X.Y and FL.Zh. collected the data. XY.F. revised the data. Ch.Zh. and L.Sh. contributed to data collection. All authors have read the manuscript and approve the final version.

Competing interests

The authors declare no competing interests.

Additional information

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