

Subclinical Thyroid Dysfunction and Incident Hip Fracture in Older Adults

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Background: Subclinical thyroid dysfunction is common in older adults and affects bone metabolism, but its effects on fracture risk have not been reported. We sought to determine prospectively whether older men and women with subclinical hyperthyroidism or hypothyroidism have an increased risk of hip fracture.

Methods: Prospective cohort of 3567 US community-dwelling adults, 65 years or older, with biochemically defined subclinical thyroid dysfunction or euthyroidism was enrolled from June 10, 1989, through May 30, 1990, and followed up through 2004. Main outcome measures included incidence and hazard ratios (HRs), with 95% confidence intervals (CIs), of confirmed incident hip fractures for groups with subclinical hypothyroidism, subclinical hyperthyroidism, and euthyroidism as defined at baseline.

Results: During 39 952 person-years (median follow-up, 13 years), hip fracture incidence (per 1000 men-years) was 13.65 in men with subclinical hyperthyroidism (n=29) and 10.27 in men with subclinical

hypothyroidism (n=184), both greater than 5.0 in men with euthyroidism (n=1159). Men with subclinical hypothyroidism had a multivariable-adjusted HR of 2.31 (95% CI, 1.25-4.27); those with subclinical hyperthyroidism, 3.27 (0.99-11.30). After excluding those with baseline use of thyroid-altering medications, men with endogenous subclinical hyperthyroidism had a higher HR of 4.91 (95% CI, 1.13-21.27), as did men with endogenous subclinical hypothyroidism (2.45, 1.27-4.73). Hip fracture incidence (per 1000 women-years) was 8.93 in women with subclinical hypothyroidism (n=359) and 10.90 in women with subclinical hyperthyroidism (n=142) compared with 10.18 in women with euthyroidism (n=1694). No clear association between subclinical dysfunction and fracture was observed in women.

Conclusions: Older men with subclinical hyperthyroidism or hypothyroidism are at increased risk for hip fracture. Whether treatment of the subclinical syndrome reduces this risk is unknown.

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OVERT HYPERTHYROIDISM has long been recognized as a risk factor for low bone mineral density (BMD) and osteoporotic fracture in older women.^{1,2} However, the relationship between biochemically defined subclinical hypothyroidism or hyperthyroidism and fracture risk is not known. Subclinical thyroid dysfunction is much more common than overt dysfunction, especially in older adults.³ Subclinical hypothyroidism (high levels of thyrotropin [TSH], with levels of free thyroxine [FT₄] within the reference range) prevails in 8% to 10% and in 17% of women aged 45 to 74 years and 75 years or older, respectively,⁴ and in 6.2% of men older than 65.⁴ Subclinical hyperthyroidism (low TSH levels, with FT₄ levels within the reference range) is less common (about 1% of men and 1.5% in women older than 60 years).³

Studies of the relationship between thyroid function and fracture risk have been specific to women, and most did not measure biochemical thyroid function.^{3,5,6} One

large prospective fracture study assessed biochemical evidence for overactive thyroid in older women, reporting that those with very low serum TSH levels (≤ 0.1 mIU/L) had an increased risk of hip fracture.⁷ However, FT₄ levels were not available to discern subclinical from overt hyperthyroidism, and the study was conducted in women only. Biologically, TSH and FT₄ may have direct effects on bone skeleton and metabolism.^{8,9} In patients with subclinical hyperthyroidism, minor changes in thyroid hormone and/or TSH levels can worsen BMD.¹⁰ Recent biological studies have shown that a lack of thyroid hormone can impair bone formation, decrease bone turnover, and lead to bone fragility.¹¹⁻¹³

Experts continue to debate the management of subclinical hypothyroidism and hyperthyroidism owing to the absence of sufficient evidence of clinically meaningful health effects.^{3,14-17} No prospective studies in men or women have reported on biochemically defined subclinical hypothyroidism or hyperthyroidism and fracture risk. Moreover, better clinical predictors of

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hip fracture are needed in men because BMD-defined osteoporosis is much less sensitive for hip fracture in men than in women.¹⁸ In the present study, we aimed to determine whether biochemically defined subclinical hypothyroidism and hyperthyroidism are independent risk factors of subsequent hip fracture in older men and women.

METHODS

STUDY PARTICIPANTS

The Cardiovascular Health Study (CHS) is a prospective community-based cohort study of older men and women (aged ≥ 65 years) designed to determine the factors that predict cardiovascular disease. Details about the study were published previously.¹⁹ Briefly, from June 10, 1989, through May 30, 1990, a total of 5201 eligible participants were recruited from 4 US communities. Until 1999, semiannual contacts alternated between clinical examinations and telephone contacts, such that a clinical examination and a telephone contact occurred annually. During the telephone contact, information about hospitalizations (eg, for hip fractures) and potential cardiovascular events was collected. Major examination components were repeated during annual examinations through 1999. Medical and personal history, including medication use, was collected annually. From 1999 to 2004, participants were contacted twice a year by telephone to collect medication data, including thyroid and antiosteoporosis medications, and to identify all hospitalizations (eg, for hip fractures) and potential cardiovascular events.

BIOCHEMICAL THYROID HORMONE LEVEL MEASUREMENTS

At the initial CHS visit, blood was drawn after a 12-hour fast, and the serum samples were frozen at -70°C for future use. In banked baseline serum samples, biochemical thyroid function tests were performed at the Nuclear Medicine In Vitro Laboratory of The Johns Hopkins Hospital (Baltimore, Maryland) from 1991 through 1993. Serum TSH concentration was measured using a chemiluminescent immunometric assay (LumaTag hTSH; Nichols Institute, San Juan Capistrano, California) with a functional sensitivity (ie, the concentration at which interassay coefficient of variation is 20%) of 0.008 mIU/L and assay reference range of 0.1 to 4.5 mIU/L. Free thyroxine concentration was measured using a direct monoclonal antibody assay (Amerlex-MAB; Amersham International, Amersham, England) with a reference range of 0.7 to 1.7 ng/dL (to convert to picomoles per liter, multiply by 12.871).

Of the 3699 participants who had stored serum available in 1991, we found that 3678 (99.4%) had sufficient serum for TSH analysis. Participants who underwent TSH analysis were more likely to be women (61.77%) than those who did not (51.3%). Those undergoing and not undergoing testing did not differ by mean age, annual income, use of thyroid medication, or the proportion with a subsequent hip fracture. Of the 3646 study participants with a TSH concentration result, 701 had a TSH concentration outside the reference range and, of these, 671 (95.7%) had sufficient serum to then undergo measurement of serum FT₄ levels.

Among the 3646 participants, findings in 3567 were classifiable as euthyroidism, subclinical hyperthyroidism, or subclinical hypothyroidism and were the focus of this analysis. The following categories for subclinical thyroid dysfunction and euthyroidism were published previously²⁰:

1. Subclinical hyperthyroidism (n=171): A TSH level of less than 0.45 mIU/L with a FT₄ level in the reference range (0.7-1.7 ng/dL). Of these participants, the TSH level was less than 0.1 mIU/L in 47;

2. Euthyroidism (n=2853): A TSH level in the reference range (0.45-4.50 mIU/L); and

3. Subclinical hypothyroidism (n=543): A TSH level of 4.5 to 20.0 mIU/L with an FT₄ level in the reference range (0.7-1.7 ng/dL).

We excluded 62 adults with overt hypothyroidism (a TSH level >20 mIU/L or a TSH level >4.50 mIU/L with an FT₄ level <0.7 ng/dL) and 17 with overt hyperthyroidism (a TSH level <0.10 mIU/L and an elevated FT₄ level) from subclinical dysfunction analyses.

ASCERTAINMENT OF HIP FRACTURE EVENTS

Participants were queried by telephone interview or clinic visit every 6 months about incident fractures. Diagnoses of incident hip fractures were ascertained from hospital medical record review using codes from the *International Classification of Diseases, Ninth Revision*.

ASSESSMENT OF COVARIATES

Demographic and anthropometric factors, including putative risk factors for nontraumatic fractures, were obtained at baseline and during follow-up. We assessed age, sex, self-described race/ethnicity, weight, height, calculated body mass index, age at menopause, parity, smoking status (never, former, or current), self-reported health status, alcohol use, and fasting plasma glucose level. Frailty status was based on a well-established index of 5 components: unintentional weight loss, exhaustion, physical inactivity, low walking speed, and low hand grip strength.²¹ Self-reported leisure time physical activity, expressed in kilocalories per week, was validated by the Minnesota Heart Survey.²² Use of thyroid-altering medications, including most commonly thyroid hormones (thyroxine [T₄] and triiodothyronine [T₃]), antithyroid hormones, corticosteroids, estrogens, lithium, and amiodarone, was assessed at baseline and annually during follow-up. Personal medical history and use of antiosteoporosis medications (bisphosphonates, selective estrogen receptor modulators, parathyroid hormone, or calcitonin) and thiazides were obtained at baseline and during follow-up. Diabetes mellitus was defined as having a fasting glucose level of less than 126 mg/dL (to convert to millimoles per liter, multiply by 0.0555) or taking antidiabetes medication.

STATISTICAL ANALYSES

In this post hoc prospective analysis, baseline characteristics were summarized according to incident hip fracture status at the end of follow-up (end date, June 30, 2004) and compared using 2-sided *t* tests for mean values and χ^2 tests for percentages. Years of observation at risk were defined from baseline to date of a hip fracture, death, or last contact, whichever occurred first. Incidence rates of hip fracture were calculated by dividing the number of participants who developed a hip fracture by the person-years of observation at risk. For binary data, the 95% confidence interval (CI) computation is based on Wilson's method.²³ Kaplan-Meier curves were plotted to show the hip fracture-free time distribution by thyroid category.

Age-adjusted and multivariable Cox regression models stratified by sex (decided a priori) were used to estimate the hazard ratios (HRs) and 95% CIs of incident hip fracture associated with subclinical hypothyroidism and hyperthyroidism, separately, compared with euthyroidism. To assess whether subclinical hypothyroidism and hyperthyroidism are independent risk factors for subsequent hip fracture, potential confounders and fracture risk factors were included in multivariable models. Hazard estimates are shown for all men and

women who had biochemically defined subclinical thyroid dysfunction or euthyroidism. To assess the relationship between endogenous subclinical thyroid dysfunction and fracture risk, analyses were repeated after excluding participants taking thyroid-altering medications at baseline.

Before Cox analyses, the assumption of proportional hazards was tested and met graphically and numerically using scaled Schoenfeld residuals.²⁴ Multivariable models used information about each participant's entry time, end time, event status, and covariate status. Multivariable models included adjustment for the use of antiosteoporosis or thyroid-altering medications (predominantly thyroid hormone) during follow-up as time-varying covariates. Whenever a medication status changed annually during follow-up, the participant's information was split into 2 records, with updated end time in the first entry and updated covariates (without a fracture event) in the second entry.

Frailty index status, which includes measures of weakness in muscle and fall potential, was included in models to determine whether HR estimates were attenuated with its inclusion as a potential mediator. Because biochemical thyroid function testing was performed post hoc in stored baseline serum, participants did not receive their results and thus no bias to subsequent monitoring or treatment was introduced. A 2-sided $P < .05$ was considered statistically significant for a main association.

RESULTS

BASELINE CHARACTERISTICS AND INCIDENT HIP FRACTURE

The 3678 study participants (2270 women and 1408 men; mean age, 73 years) who underwent biochemical TSH testing accrued 39 952 person-years during a median follow-up of 13 (interquartile range, 7.8-14.5) years. In men, the cumulative incidence of hip fracture (per 1000 person-years) was 5.74 (95% CI, 4.62-7.13) and in women, 9.79 (8.66-11.07). Men and women who had a subsequent hip fracture had a lower baseline weight and body mass index and were older than those who did not (**Table 1**). Most participants were white. A lower proportion of women with fractures were black than those who did not have them.

Subclinical hypothyroidism (14.9%) was about 3 times more common than subclinical hyperthyroidism (4.7%). Overt hypothyroidism was present in 1.7% and overt hyperthyroidism in 0.5% of all participants. Thyroid function status differed by fracture status in men ($P = .03$); subclinical hypothyroidism and hyperthyroidism were more common in men with fractures. Overt thyroid dysfunction was present in only 1.2% and was excluded in subsequent analyses. Baseline use of medications that alter thyroid metabolism did not differ by fracture status ($P = .64$).

BASELINE CHARACTERISTICS AND SUBCLINICAL THYROID DYSFUNCTION

Of the 3567 participants with classifiable subclinical thyroid dysfunction or euthyroidism, 1372 were men and 2195 were women. Among the 1372 men, 184 (13.4%) had subclinical hypothyroidism, 29 (2.1%) had subclinical hyperthyroidism, and 1159 (84.5%) had euthyroidism (**Table 2**). Among the 29 men with subclinical hyperthyroidism, 4 (13.8%) had a TSH level of less than

0.1 mIU/L and 13 (44.8%) were taking thyroid-altering medication at baseline. Of the 184 men with subclinical hypothyroidism, 9 (4.9%) were taking thyroid-altering medication at baseline.

Among the 2195 women, 359 (16.4%) had subclinical hypothyroidism, 142 (6.5%) had subclinical hyperthyroidism (43 [30.3%] had TSH levels < 0.1 mIU/L), and 1694 (77.2%) had euthyroidism (Table 2). Use of thyroid-altering medication, predominantly T4, was prevalent in 116 women with subclinical hyperthyroidism (81.7%) and 39 with subclinically hypothyroidism (10.9%). Estrogen use was prevalent in 12.5% of women with subclinical thyroid dysfunction and 16.2% with euthyroidism.

RISK OF HIP FRACTURE BY SUBCLINICAL THYROID DYSFUNCTION

We conducted 2 sets of sex-specific analyses. First, risk of hip fracture associated with subclinical thyroid dysfunction was assessed in all men and women. Second, analyses were then repeated after excluding men and women who took thyroid-altering medications at baseline to assess specifically the risk of hip fracture associated with endogenous (naturally occurring) subclinical thyroid dysfunction.

In the 1372 men, 27.5% who experienced an incident hip fracture had subclinical thyroid dysfunction at baseline. Men with subclinical hypothyroidism had an age-adjusted 1.86-fold greater hazard (95% CI, 1.09-3.16) for a subsequent hip fracture compared with men with euthyroidism (**Table 3**). Men with subclinical hypothyroidism had a 2.31-fold greater hazard (95% CI, 1.25-4.27) after adjustment for potential confounders and fracture risk factors, including time-varying covariates for any thyroid-altering medication use (137 men [10.0%]) and antiosteoporosis medication use (14 men [1.0%]) during follow-up. Subclinically hyperthyroid men had an age-adjusted 3.07-fold greater hazard (95% CI, 1.11-8.46) than men with euthyroidism, based on 4 such men with an incident hip fracture. After multivariable adjustment, subclinically hyperthyroid men had a borderline-significant 3.27-fold increased hazard, with a wide 95% CI (0.99-11.30).

Subsequently, the relationship between endogenous subclinical thyroid dysfunction and hip fracture was assessed in men. We excluded 85 men taking thyroid-altering medication at baseline. Sixteen of the 175 men with endogenous subclinical hypothyroidism experienced a hip fracture (incidence, 9.66 per 1000 person-years). Compared with euthyroidism, men with endogenous subclinical hypothyroidism had an age-adjusted 1.73-fold greater hazard (95% CI, 0.99-3.03) for hip fracture. Their hazard increased to 2.45-fold (95% CI, 1.27-4.73) after adjustment for covariates, including the use of thyroid-altering and antiosteoporosis medications during follow-up. Men with more severe subclinical hypothyroidism (ie, a TSH level ≥ 10 mIU/L) did not have a greater risk than those with a TSH level of less than 10 mIU/L (data not shown). Three of the 16 men with endogenous subclinical hyperthyroidism experienced a subsequent hip fracture (incidence, 21.09 per 1000 person-years). Men with endogenous subclinical hyperthyroidism

Table 1. Comparisons of Baseline Characteristics According to Incident Hip Fracture Status in Men and Women: Cardiovascular Health Study^a

Characteristic	All Participants (N=3678)	Men			Women		
		No Hip Fracture (n=1327)	Hip Fracture (n=81)	P Value ^b	No Hip Fracture (n=2017)	Hip Fracture (n=253)	P Value ^b
Age, mean (SD), y	72.8 (5.6)	73.3 (5.8)	75.8 (5.7)	<.001	72.1 (5.3)	74.4 (5.7)	<.001
Black race	183 (5.0)	65 (4.9)	2 (2.5)	.47	112 (5.6)	4 (1.6)	.01
Weight, mean (SD), kg	71.1 (14.2)	79.0 (11.9)	75.2 (10.1)	<.001	66.9 (13.5)	62.3 (12.0)	<.001
Height, mean (SD), cm	164.3 (9.4)	173.0 (6.6)	173.7 (5.7)	.31	158.8 (6.2)	158.8 (6.5)	.97
BMI, mean (SD)	26.2 (4.5)	26.3 (3.5)	24.9 (3.0)	<.001	26.5 (5.1)	24.6 (4.2)	<.001
Alcohol use per week							
None	1482 (40.5)	376 (28.5)	33 (40.7)	.14	943 (47.1)	130 (52.0)	.59
Former drinkers	291 (8.0)	158 (12.0)	10 (12.3)				
<1 Drink	745 (20.4)	233 (17.6)	9 (11.1)				
1-6 Drinks	616 (16.9)	290 (22.0)	17 (21.0)				
≥7 Drinks	521 (14.3)	264 (20.0)	12 (14.8)				
Cigarette smoking							
Never	1776 (48.3)	426 (32.2)	31 (38.3)	.43	1168 (57.9)	151 (59.7)	.82
Former	1510 (41.1)	783 (59.1)	42 (51.9)				
Current	389 (10.6)	116 (8.8)	8 (9.9)				
Thiazide use	686 (18.7)	201 (15.1)	8 (9.9)	.26	425 (21.1)	52 (20.6)	.91
Diabetes mellitus	513 (13.9)	229 (17.3)	11 (13.6)	.48	241 (11.9)	32 (12.6)	.83
≥1 Live birth	1857 (81.8)	NA	NA		1656 (82.1)	201 (79.4)	.04
Age at menopause, mean (SD), y	47.1 (6.7)	NA	NA		47.1 (6.7)	47.1 (6.5)	.89
Estrogen use		NA	NA				
Never	1339 (59.0)			.43	1174 (58.2)	165 (65.2)	.10
Past	644 (28.2)						
Current	287 (12.6)						
Calcium supplement intake	810 (22.0)	135 (10.2)	11 (13.6)	.43	594 (29.4)	70 (27.7)	.61
Physical activity, mean (SD), kcal/d	1781 (2051)	1961 (2081)	1842 (2153)	.63	1661 (2023)	1771 (2023)	.42
Frailty status							
Not frail	1609 (48.2)	595 (49.3)	30 (43.5)	.64	877 (47.9)	107 (45.9)	.16
Intermediate	1513 (45.3)	548 (45.4)	35 (50.7)				
Frail	217 (6.5)	64 (5.3)	4 (5.8)				
Health status, self-reported							
Excellent/very good	839 (22.8)	294 (22.2)	17 (21.2)	.82	467 (23.2)	61 (24.2)	.30
Good	1353 (36.9)	483 (36.5)	32 (40.0)				
Fair/poor	1477 (40.2)	546 (41.3)	31 (38.8)				
Antihypertensive medication	8 (0.2)	0	0		8 (0.4)	0	.66
Thyroid-altering medication	417 (11.3)	87 (6.6)	6 (7.4)	.94	290 (14.4)	34 (13.4)	.76
Thyroid hormone medication	339 (9.2)	51 (3.8)	5 (6.2)	.45	253 (12.5)	30 (11.9)	.83
T4	245 (72.3)	39 (76.5)	3 (60.0)		182 (71.9)	21 (70.0)	
T3	4 (1.2)	1 (2.0)	0		3 (1.2)	0	
T4 and T3	88 (26.0)	11 (22.0)	2 (40.0)		67 (26.5)	8 (26.7)	
Unknown type	4 (1.2)	0	0		1 (0.4)	1 (3.3)	
Antithyroid or corticosteroid medication ^c	92 (2.5)	36 (2.7)	1 (1.2)	.65	51 (2.5)	4 (1.6)	.51
Thyroid function							
Overt hypothyroidism	62 (1.7)	21 (1.6)	1 (1.2)	.03	39 (2.0)	1 (0.4)	.39
Subclinical hypothyroidism	543 (14.9)	166 (12.6)	18 (22.2)				
Euthyroidism	2853 (78.3)	1101 (83.5)	58 (71.6)				
Subclinical hyperthyroidism	171 (4.7)	25 (1.9)	4 (4.9)				
Overt hyperthyroidism	17 (0.5)	5 (0.4)	0				

Abbreviations: BMI, body mass index (calculated as the weight in kilograms divided by height in kilograms squared); NA, not applicable; T3, triiodothyronine; T4, thyroxine.

^aUnless otherwise indicated, data are expressed as number (percentage) of patients. Data were missing for some characteristics; therefore, sums may not match the numbers given in the column headings. Percentages are based on the total for each characteristic and, because of rounding, may not sum to 100.

^bDetermined with 2-sided *t* tests for mean values and χ^2 tests for percentages.

^cIndicates antithyroid hormone (n=1) or corticosteroid (n=91) medication use in men and women.

had a nearly 5-fold age-adjusted hazard for hip fracture than those with euthyroidism (HR, 4.95; 95% CI, 1.54-15.86). This hazard magnitude was unchanged after adjustment for covariates, including use of thyroid-altering medications during follow-up, but the 95% CIs around these HRs were wide.

Analogous analyses were performed in women. In all, 2195 women with subclinical hypothyroidism or hyperthyroidism did not have an increased or decreased hazard for hip fracture, even after multivariable adjustment, including time-varying follow-up use of thyroid-altering medications (506 women [23.1%]) and antihypertensive medi-

Table 2. Baseline Characteristics of Women and Men With Baseline Measurement of TSH Levels: Cardiovascular Health Study^a

Baseline Characteristics	Men			Women		
	Subclinical Hyperthyroidism (n=29)	Euthyroidism (n=1159)	Subclinical Hypothyroidism (n=184)	Subclinical Hyperthyroidism (n=142)	Euthyroidism (n=1694)	Subclinical Hypothyroidism (n=359)
TSH, mean (SD), mIU/L	0.22 (0.15)	2.08 (0.96)	6.66 (2.57)	0.17 (0.12)	2.26 (1.02)	6.78 (2.58)
Thyroid hormone medication	11 (37.9)	31 (2.7)	6 (3.3)	108 (76.1)	114 (6.7)	34 (9.5)
T4	7 (63.6)	24 (77.4)	5 (83.3)	72 (66.7)	84 (73.7)	29 (85.3)
T3	0	0	0	2 (1.9)	0	0
T4 and T3	4 (36.4)	7 (22.6)	1 (16.7)	34 (31.5)	29 (25.4)	4 (11.8)
Unknown type	0	0	0	0	1 (0.9)	1 (2.9)
Antithyroid or corticosteroid medication ^b	2 (6.9)	32 (2.8)	3 (1.6)	8 (5.6)	41 (2.4)	5 (1.4)

Abbreviations: T3, triiodothyronine; T4, thyroxine; TSH, thyrotropin.

^aUnless otherwise indicated, data are expressed as number (percentage) of participants.

^bOne woman with subclinical hypothyroidism took antithyroid medication, and the rest took corticosteroid medication.

Table 3. Incidence Rates of Hip Fractures and HR Estimates of Hip Fracture Associated With Subclinical Thyroid Function Status in Men and Women: Cardiovascular Health Study

	Men			Women		
	Subclinical Hyperthyroidism	Euthyroidism	Subclinical Hypothyroidism	Subclinical Hyperthyroidism	Euthyroidism	Subclinical Hypothyroidism
All men (N=1372)						
No. at risk	29	1159	184	142	1694	359
No. (%) of events	4 (13.8)	58 (5.0)	18 (9.8)	17 (12.0)	198 (11.7)	36 (10.0)
Incidence per 1000 person-years (95% CI)	13.65 (5.32-34.56)	4.96 (3.84-6.40)	10.27 (6.50-16.17)	10.90 (6.82-17.39)	10.18 (8.86-11.69)	8.93 (6.46-12.34)
HR (95% CI)						
Age-adjusted	3.07 (1.11-8.46)	1 [Reference]	1.86 (1.09-3.16)	1.06 (0.65-1.74)	1 [Reference]	0.87 (0.61-1.24)
Multivariable model 1 ^a	2.57 (0.79-8.38)	1 [Reference]	2.03 (1.13-3.66)	0.96 (0.52-1.78)	1 [Reference]	0.74 (0.48-1.13)
Multivariable model 2 ^b	3.27 (0.99-11.30)	1 [Reference]	2.31 (1.25-4.27)	1.36 (0.66-2.81)	1 [Reference]	0.87 (0.55-1.36)
Participants not taking thyroid-altering medication at baseline (n=1287) ^c						
No. at risk	16	1096	175	34	1543	321
No. (%) of events	3 (18.8)	55 (5.0)	16 (9.1)	4 (11.8)	184 (11.9)	30 (9.3)
Incidence per 1000 person-years (95% CI)	21.09 (7.02-60.17)	4.94 (3.80-6.42)	9.66 (5.96-15.64)	11.12 (4.33-28.25)	10.36 (8.97-11.95)	8.20 (5.75-11.68)
HR (95% CI)						
Age-adjusted	4.95 (1.54-15.86)	1 [Reference]	1.73 (0.99-3.03)	0.98 (0.36-2.64)	1 [Reference]	0.79 (0.54-1.16)
Multivariable model 1 ^a	4.56 (1.06-19.64)	1 [Reference]	1.84 (0.98-3.43)	1.70 (0.54-5.38)	1 [Reference]	0.70 (0.45-1.10)
Multivariable model 2 ^b	4.91 (1.13-21.27)	1 [Reference]	2.45 (1.27-4.73)	2.42 (0.84-6.31)	1 [Reference]	0.87 (0.54-1.41)

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

^aAdjusted for age, race, self-reported health status, frailty status, smoking, alcohol use, height, weight, and calcium supplementation.

^bAdjusted for multivariable model 1 covariates plus time-varying covariates for use during follow-up of antiosteoporosis medication (for men: 13 of 1327 noncases [1.0%] and 1 of 81 cases [1.2%]) and thyroid-altering medication (for men: 127 of 1327 noncases [9.6%] and 10 of 81 cases [12.3%]; for women: 200 of 2017 noncases [9.9%] and 41 of 253 cases [16.2%]) and thyroid-altering medication (454 of 2017 noncases [22.5%] and 52 of 253 cases [20.6%]).

^cExcludes 85 men and 297 women taking thyroid-altering medication at baseline (thyroid hormones, antithyroid hormones, and corticosteroids). None were taking amiodarone or lithium.

cations (241 women [11.1%]) during follow-up (Table 3). The prevalence of TSH levels of less than 0.1 mIU/L was 3.2% among women who fractured their hip. To evaluate the relationship between endogenous subclinical thyroid dysfunction and the risk of hip fracture, 297 women were excluded because they were taking thyroid-altering medication at baseline. No clear association was observed. Women with endogenous subclinical hyperthyroidism had a multivariable-adjusted 2.42-fold (95% CI, 0.84-6.31) greater hazard than those with euthyroidism, but this estimate did not reach statistical significance and the CI was wide, possibly reflecting the small number of fractures (n=4) in this subgroup.

Adding history of falls or frailty status, including measures of muscle strength and correlates of fall potential, to the Cox models changed the HR estimates by less than 10%. Thus, frailty and falls did not appear to mediate the observed associations between subclinical thyroid dysfunction and hip fracture.

COMMENT

Debate about clinical management of subclinical thyroid dysfunction continues.^{3,14-16,25,26} We conducted this

study to address the absence of sufficient studies of clinically meaningful health effects.^{3,14-17} Potential cardiovascular consequences garner the most attention; however, potential deleterious effects on bone and future fracture risk is a major knowledge gap. Moreover, clinical predictors in men other than BMD need to be identified.¹⁸ To our knowledge, this post hoc prospective analysis is the first large prospective study to assess hip fracture risk associated with biochemically defined subclinical thyroid dysfunction in both older women and men. Older men with biochemically defined subclinical hypothyroidism and hyperthyroidism had an increased risk of hip fracture. Most of the men with subclinical hypothyroidism had a TSH level of less than 10 mIU/L, suggesting that even mild subclinical hypothyroidism is deleterious. The associated magnitudes of fracture risk (2- to nearly 5-fold) in older men are at least as great as those associated with a 1-SD decrease in BMD at the hip in older men.¹⁸ Moreover, the increased risks did not clearly depend on whether subclinical dysfunction was endogenous or exogenous. A prospective study of 5876 older men observed that a self-reported physician diagnosis of low thyroid hormone level was associated with an increased risk of fracture in univariate but not multivariable analyses.²⁷ Biochemical thyroid function testing was not reported in that study.

The present study results differed between older men and women. Reasons for this are not clear. Perhaps subclinical dysfunction is less recognized in men, and both thyroid dysfunction and osteoporosis are more recognized and treated in women. However, accounting for use of thyroid-altering and antiosteoporosis medications in this study was meant to address this possibility. Another possibility that may warrant future study is that subclinical thyroid dysfunction physiologically increases bone fragility and related fractures disproportionately more in men than in women. Somewhat surprisingly, no increased risk of hip fracture in women was observed. Subclinically hyperthyroid women had an HR of 2.42, but this was not statistically significant. The Study of Osteoporotic Fractures in older women reported that a very low TSH level (<0.1 mIU/L) was associated with a significant 3.6-fold increased hazard for subsequent hip fracture and a possible intermediate risk when TSH is within the range of 0.1 to 0.5 mIU/L.⁷ Women from the present study and the Study of Osteoporotic Fractures were comparable in age, weight, and use of thyroid-altering medications. The prevalence of TSH levels of less than 0.1 mIU/L was lower among women who fractured their hip in the present study (3.2%) than among those in the Study of Osteoporotic Fractures (9.5%), suggesting that subclinical thyroid dysfunction was milder in the present study.

Rodent studies suggest that abnormal levels of TSH and FT₄ may independently affect bone integrity by uncoupling bone remodeling.^{8,28-31} Thyroid hormone acts on osteoblasts and osteoclasts to increase bone turnover, leading to net bone loss.³¹ Thyrotropin might decrease bone turnover, although this remains controversial.^{32,33} It might bind directly to TSH receptors on osteoblast and osteoclast precursors to suppress osteoclast formation and bone resorption and to stimulate

osteoblast differentiation.^{8,34} Thyrotropin receptor-knockout mice experience high bone turnover in which resorption outpaces formation.⁸ Ovariectomized rats given TSH have less bone loss³⁵ and improved bone volume, microarchitecture, and strength.³⁴ These observations need to be confirmed in humans, but it is plausible that lower TSH and higher FT₄ levels (as in subclinical hyperthyroidism) increase bone turnover, BMD loss, and the risk of fragility fractures.^{8,9,28} Also in hyperthyroidism, muscle catabolism could lead to muscle weakness and consequent falls/fractures. Conversely, the mechanism of higher TSH and lower FT₄ levels (as in subclinical hypothyroidism) on bone integrity is unclear but could impair bone quality or neuromuscular action, contributing to falls/fractures. In this study, frailty, muscle weakness, and falls did not appear to mediate the observed associations between subclinical thyroid dysfunction and fracture risk in men.

This study has limitations. Thyroid function testing took place at a single point, so change in thyroid function could not be assessed. The number of participants with subclinical dysfunction and those with fracture were relatively small despite a large study population. The number of participants taking thyroid-altering medication was small, limiting statistical power to assess this subgroup; however, after excluding these participants or adjusting for such medication use in multivariable models, results remained consistent. Although history of thyroid dysfunction, duration of thyroid medication use, and history of fractures before baseline were unknown, the use of thyroid-altering medications and antiosteoporosis medications was evaluated at baseline and annual follow-up. Bone mineral density was not available for this analysis; therefore, BMD as a potential mediator between subclinical thyroid dysfunction and hip fracture could not be determined. This study, based on its observational design, cannot address directly whether normalization of subclinical thyroid dysfunction in older men or women reduces fracture risk.

This study has major strengths. It is the first and largest prospective, community-based study of its kind, with biochemically defined subclinical thyroid function in older adults. This study introduces subclinical hypothyroidism and hyperthyroidism as predictors of hip fracture in older men. The 2- to nearly 5-fold hazard estimates are at least as great as that for a 1-SD decrease in BMD in men.¹⁸ This study collected information about the use of thyroid-altering medications, an important consideration in assessing subclinical thyroid dysfunction, especially in older adults.³⁶ It also verified incident hip fracture events in a well-characterized cohort.

This study was conducted to address the absence of sufficient studies of clinically meaningful health effects and the ongoing clinical debate on how to best manage subclinical thyroid dysfunction.^{3,14-17} In clinical practice, cardiovascular disorders and osteoporotic fractures are leading long-term concerns in patients with subclinical dysfunction, particularly subclinical hyperthyroidism. The CHS reported previously that subclinical hyperthyroidism is associated with the development of atrial fibrillation but did not support that subclinical thyroid dysfunction was related to other

cardiovascular disorders, including coronary heart disease and cerebrovascular disease, and to mortality.²⁰ Per the CHS, heart failure is an important marker for hip fracture risk, largely because of shared comorbidities and risk factors.³⁷ Thyroid medication use was not a factor, but whether subclinical thyroid function potentiates the association between heart failure and hip fracture risk needs further study. From the present study, we estimated a 13% attributable risk of hip fracture due to thyroid dysfunction in older men during the entire follow-up period in this study.

In summary, this study indicates that subclinical hypothyroidism and hyperthyroidism are independent predictors of hip fracture in older men. Subclinical hypothyroidism has not been linked previously to fracture. This study suggests that older men with subclinical hyperthyroidism and hypothyroidism, including mild subclinical hypothyroidism (TSH level, <10 mIU/L), should undergo clinical evaluation regarding their risk of hip fracture. Future studies should address directly whether correction of subclinical thyroid dysfunction in these men will reduce their hip fracture risk. If confirmed, these study results will provide evidence to guide clinical recommendations about subclinical thyroid dysfunction.

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