The Thyroid Epidemiology, Audit, and Research Study (TEARS): Morbidity in Patients with Endogenous Subclinical Hyperthyroidism

Thenmalar Vadiveloo, Peter T. Donnan, Lynda Cochrane, and Graham P. Leese

Dundee Epidemiology and Biostatistics Unit (T.V., P.T.D., L.C.), Division of Clinical and Population Sciences and Education, and Department of Medicine (G.P.L.), University of Dundee, Dundee, Scotland, United Kingdom

Objective: Our objective was to investigate the long-term outcomes for patients with endogenous subclinical hyperthyroidism (SH).

Design: Population record-linkage technology was used retrospectively to identify patients with SH and hospital admissions from January 1, 1993, to December 31, 2009.

Patients: All Tayside residents over 18 yr old with at least two serum TSH measurements below the reference range for at least 4 months apart and normal free T_4/total T_4 and normal total T_3 concentrations at baseline were included as potential cases. Using a unique patient identifier, data linkage enabled a cohort of SH cases to be identified from biochemistry, prescription, admission, and radioactive iodine treatment records matched to five comparators from the general population.

Outcome Measures: The association between endogenous SH and cardiovascular disease, fracture, dysrhythmia, dementia, and cancer was assessed.

Results: Compared with the reference population, SH was associated with an increased risk of nonfatal cardiovascular morbidity, osteoporotic fracture, dysrhythmia, and dementia, with adjusted hazard ratios (HR) of 1.39 (1.22–1.58), 1.25 (1.04–1.50), 1.65 (1.26–2.17), and 1.64 (1.20–2.25), respectively. When SH patients who developed overt hyperthyroidism during follow-up were excluded, SH patients were associated with an increased risk of cardiovascular morbidity [HR = 1.36 (1.19–1.57)], dysrhythmia [HR = 1.39 (1.02–1.90)], and dementia [HR = 1.79 (1.28–2.51)] but not fracture and cancer.

Conclusion: Patients with endogenous SH have an increased risk of cardiovascular disease and dysrhythmia. There is an association with fracture and dementia that is not related to TSH concentration and therefore is less likely to be causally related. No association was found between SH and cancer. (***J Clin Endocrinol Metab*** **96: 1344–1351, 2011)**

Subclinical hyperthyroidism is defined by low or suppressed TSH with free T_4 (FT_4) and FT_3 concentration within the reference range. It is more common in women than men, and its incidence increases with advancing age. We have recently reported a prevalence of subclinical hyperthyroidism in Tayside, Scotland, of 0.63% with an incidence of 29 per 100,000 (1). This is similar to other areas that reported a prevalence of 0.7–12.4% (2–4).

Although individuals with overt hyperthyroidism are known to have an increased risk of cardiovascular disease, osteoporotic-related fractures, and cardiac dysrhythmia (5), the clinical outcome of patients with subclinical hyperthyroidism remains unclear. The association between

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2010-2693 Received November 15, 2010. Accepted January 31, 2011.
First Published Online February 23, 2011

Abbreviations: AUROC, Area under the Receiver Operating Characteristic; CHI, Community Health Index; CI, confidence interval; FT_4, free T_4; HR, hazard ratio; ICD, International Classification of Diseases; SIMD, Scottish Index of Multiple Deprivation; SMR01, Scottish morbidity record 1.

subclinical hyperthyroidism and clinical outcomes differs among studies. Some have reported that subclinical hyperthyroidism is associated with an increased risk for coronary heart disease (6, 7). However, some others have reported no association between cardiovascular risk and subclinical hyperthyroidism (8, 9). Similarly, the reported association between subclinical hyperthyroidism and fracture in the literature is variable (10). Földes *et al.* (11) reported that endogenous subclinical hyperthyroidism resulted in a significant decrease in bone mineral density among postmenopausal women, but Bauer *et al.* (12) reported that low TSH levels were not associated with bone loss in older ambulatory women. The definitions of subclinical hyperthyroidism and the follow-up of patients vary between these studies and might explain some of the differences.

The aim of this study was to investigate exclusively patients with endogenous subclinical hyperthyroidism who had not had previous thyroid disease and to exclude patients who developed subsequent overt hyperthyroidism. The aim was to see whether they had an increased risk of nonfatal cardiovascular disease, osteoporotic fracture, dysrhythmia, dementia, or cancer and whether there is a difference between patients with differing levels of serum TSH concentrations.

Patients and Methods

Patients

All Tayside residents registered with a general practice in Scotland are assigned to a unique 10-digit health index, known as a Community Health Index (CHI). CHI is used as a patient identifier that facilitates the linkage of all health care-related records. All such records are held and linked at the Health Informatics Centre (http://www.dundee.ac.uk/hic) of the University of Dundee (1, 13, 14). We have previously identified patients between January 1993 and December 2009 with endogenous subclinical hyperthyroidism using eight principle anonymous patient-level datasets, and the patient selection and classification process is described in detail in Vadiveloo *et al.* (1). In brief, patients were identified from the Tayside population based on at least two measurements of TSH below the reference range (≤0.4 mU/liter) with a minimum of a 4-month interval between measurements. In addition, cases had normal FT_4/T_4 (FT_4 = 10–25 pmol/liter; total T_4 = 65–155 nmol/liter) and total T_3 (0.9–2.6 nmol/liter) concentrations at baseline. Exclusion criteria included 1) any patient younger than 18 yr old at baseline; 2) any patient taking T_4, carbimazole, propylthiouracil, amiodarone, and liothyronine before and during the first year after the first abnormal TSH result; 3) any patient taking amiodarone, liothyronine, and thyroxine (without carbimazole or propylthiouracil) during the study period; 4) any patient treated with radioactive iodine before and during the first year after the first abnormal TSH results; 5) any patient who had previously undergone thyroid surgery before and during the first year after the first abnormal TSH results (OPCS code B08/B09); and 6) any patient who was pregnant at the time of the first abnormal TSH result.

In this study, cases with pituitary disorder were also excluded from the study by excluding any patients on long-term low-dose hydrocortisone treatment. Patients were then classified into two categories: those with TSH measurements between 0.1 and 0.4 mU/liter (group 1) and those with TSH measurements less than 0.1 mU/liter (group 2) based on their TSH concentrations over a 6-month duration. All patients had subclinical hyperthyroidism at baseline, but some patients may have developed overt hyperthyroidism or reverted to normal during the follow-up period. Thus, the long-term outcome of patients who remained subclinical hyperthyroid during the study period was also investigated. In this subgroup, patients were also excluded if they 1) were taking any antithyroid treatments (drugs and radioactive iodine) during the study period; 2) had low TSH (<0.4 mU/liter) and high FT_4/T_4 and T_3 measurements indicating hyperthyroidism; or 3) had normal TSH (0.4–4.0 mU/liter), FT_4 (10–25 pmol/liter), T_4 (65–155 nmol/liter), and T_3 (0.9–2.6 nmol/liter) concentrations.

Databases and data validity

Tayside population demographic database

This served as a master index to provide information on gender, date of birth, date of death, and dates registered with general practitioner. This information was obtained from the National CHI register and contained 99% of the population. There was a validation done by the external systems before it reached the Health Informatics Centre.

Biochemistry database

This contained all thyroid function tests, TSH, FT_4, total T_4, and total T_3 during our study period. Each entry comprised the patient's anonymized CHI, the test performed, date, and the results. These data were received directly from the lab systems and were validated routinely.

Scottish morbidity record 1 (SMR01)

The SMR01 dataset was used to obtain information on morbidity. This dataset consisted of hospital admission data routinely validated and collated by the Information and Statistics Division of the National Health Service in Scotland (http://www.isdscotland.org/isd/2737.html). The International Classification of Diseases (ICD) ninth and 10th revision codes are used in the SMR01 to classify all hospital inpatient episodes.

Tayside prescription database

This contained all prescriptions dispensed from all community pharmacies in Tayside. Each entry comprised the patient's anonymized CHI, prescription date, drug name, formulation, dosage, frequency, and duration. These data were received from Practitioner Services Divisions.

Statistical methods

The following outcomes of all patients with subclinical hyperthyroidism were identified: nonfatal cardiovascular disease (ICD9: 390–429; ICD10: I00–I52), osteoporotic fractures (ICD9: 733.1, 805.4, 805.5, 806.4, 806.5, 813, 820, and 821; ICD10: S32, S52, S72, and M80), dysrhythmia (ICD9:

427; ICD10: I47–I49), dementia (ICD9: 290; ICD10: F00, F01, F02, and F03), and cancer (ICD9: 140–209; ICD10: C00-C99). The ICD codes for osteoporotic fractures relates to all fractures of lower back, forearm, hip, and other. These are the classic fracture sites for osteoporotic-related fractures for our definition, but we are aware that these may differ from an osteoporotic diagnosis. Survival analysis was used to follow up patients until an event occurred or they were censored or the end of the study. Cox proportional hazards model was used to model the data, and the assumption of proportional hazards was assessed by plotting log minus log plots for the baseline covariates and fitting time interactions. There was no violation of the assumption of proportional hazards in each covariate. Kaplan-Meier curves were produced to compare risk of subclinical hyperthyroid patients with the Tayside population.

The outcomes of subclinical hyperthyroid patients were compared with five matched controls (age and gender) from the Tayside population. Each comparator's start date was assigned the date of diagnosis of subclinical hyperthyroidism as defined above. The age and gender were included as strata in the model. Some data for social deprivation were missing in the dataset. These data were assumed to be missing completely at random because it represented less than 2% of the whole dataset.

Binomial logistic regression was used to examine the effects of demographic, biochemical, and clinical variables on risk of developing nonfatal cardiovascular disease, osteoporotic fractures, dysrhythmia, and dementia in subclinical hyperthyroid patients after 5 yr of diagnosis. Predictor variables considered were TSH and FT_4 concentrations at baseline, age, gender, Scottish Index of Multiple Deprivation (SIMD), diabetes, and previous history of cardiovascular disease, any fracture, dysrhythmia, dementia, cerebrovascular disease, cancer, hypertension, and renal failure. Interactions between the factors were also included. Predictive model discrimination was assessed using area under the receiver operating characteristic (AUROC) curve, which was computed using a nonparametric method. An AUROC curve of 0.5 indicates no ability to discriminate, and an area of 1.0 indicates perfect discrimination.

Other confounders

Apart from gender and age, other covariates adjusted for in the survival analysis were socioeconomic deprivation, diabetes mellitus, history of previous circulatory disease (SMR01: ICD9 390–459; ICD10 I00-I99), history of any fracture (SMR01: ICD9: 733.1, 800–829; ICD10 S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, M80, T02, T08, T10, T12), history of dysrhythmia, history of dementia, history of cancer, history of hypertension, history of renal failure, and history of psychiatric disease. Some covariates such as ethnic origin and smoking status could not be included due to lack of data available.

Ethical approval

The study was approved by the Tayside Medical Ethics Committee and data protection by the Tayside Caldicott Guardians. All analyses were performed on anonymized datasets.

Results

There were a total of 2004 patients with subclinical hyperthyroidism, of which 1491 cases had serum TSH concentrations from 0.1–0.4 mU/liter (group 1) and 414 cases had TSH concentrations below 0.1 mU/liter (group 2). The total follow-up period was 76,124 yr with a median of 2051 d (5.6 yr). Overall, 77.4% of the cases were female, and the mean age was 66.5 yr (SD 15.9). The baseline characteristics of subclinical hyperthyroid cases and reference population are shown in Table 1. At baseline, significantly higher percentages of subclinical hyperthyroid patients had diabetes ($P < 0.001$), preexisting cardiovascular disease ($P < 0.001$),

TABLE 1. Baseline characteristics of subclinical hyperthyroid cases and comparators

Covariate	All SH	SH with low TSH	SH with suppressed TSH	Comparators[a]	*P* value[b]
Patients (n)	2004	1491	414	10111	
Mean age [yr (SD)]	66.5 (15.9)	66.1 (16.0)	67.7 (15.6)	66.2 (16.5)	0.177
Female [n (%)]	1552 (77.4)	1136 (76.2)	342 (82.6)	7828 (77.4)	0.022
Diabetic [n (%)]	328 (16.4)	255 (17.1)	53 (12.8)	991 (9.8)	<0.001
SIMD category [n (%)]					
1–3 (deprived)	501 (25.0)	386 (25.9)	93 (22.5)	2104 (20.8)	
4–7	814 (40.6)	603 (40.4)	168 (40.6)	4041 (40.0)	<0.001
8–10 (affluent)	655 (32.7)	478 (32.1)	146 (35.3)	3783 (37.4)	
History of CVD [n (%)]	422 (21.1)	327 (21.9)	69 (16.7)	1182 (11.7)	<0.001
History of fracture [n (%)]	77 (3.8)	59 (4.0)	15 (3.6)	302 (3.0)	0.112
History of dysrhythmia [n (%)]	52 (2.6)	40 (2.7)	12 (2.9)	137 (1.4)	<0.001
History of dementia [n (%)]	7 (0.3)	5 (0.3)	2 (0.5)	40 (0.4)	0.898
History of cancer [n (%)]	10 (0.5)	8 (0.5)	2 (0.5)	39 (0.4)	0.674

SH, Subclinical hyperthyroidism.

[a] All cases are matched with controls based on age and gender.

[b] ANOVA for age, χ^2 test for the other categorical variables. Differences between the three groups (SH with low TSH, SH with suppressed TSH and controls) were classified as significant if *P* value < 0.05.

TABLE 2. Unadjusted and adjusted HR for inpatient admissions for cardiovascular, osteoporotic fracture, dysrhythmia, dementia, and cancer for all subclinical hyperthyroid patients

		Events		Unadjusted		Adjusted	
	Population	n	%	HR	95% CI	HR	95% CI
Nonfatal cardiovascular[b]							
All SH cases	2,004	324	16.2	1.69[a]	1.49–1.92	1.39[a]	1.22–1.58
SH with low TSH	1,491	238	16.0	1.67[a]	1.45–1.92	1.37[a]	1.18–1.58
SH with suppressed TSH	414	70	16.9	1.74[a]	1.36–2.21	1.45[a]	1.14–1.86
Comparators	10,111	943	9.3	1.00		1.00	
Osteoporotic fracture[c]							
All SH cases	2,004	152	7.6	1.37[a]	1.14–1.64	1.25[a]	1.04–1.50
SH with low TSH	1,491	112	7.5	1.36[a]	1.11–1.67	1.29[a]	1.05–1.58
SH with suppressed TSH	414	36	8.7	1.55[a]	1.10–2.17	1.23	0.88–1.73
Comparators	10,111	532	5.3	1.00		1.00	
Dysrhythmias[d]							
All SH cases	2,004	77	3.8	2.07[a]	1.58–2.70	1.65[a]	1.26–2.17
SH with low TSH	1,491	53	3.6	1.91[a]	1.40–2.59	1.52[a]	1.11–2.08
SH with suppressed TSH	414	20	4.8	2.58[a]	1.63–4.10	2.07[a]	1.30–3.29
Comparators	10,111	179	1.8	1.00		1.00	
Dementia[e]							
All SH cases	2,004	53	2.6	1.67[a]	1.22–2.29	1.64[a]	1.20–2.25
SH with low TSH	1,491	39	2.6	1.70[a]	1.20–2.42	1.77[a]	1.24–2.52
SH with suppressed TSH	414	10	2.4	1.37	0.72–2.60	1.12	0.59–2.14
Comparators	10,111	151	1.5	1.00		1.00	
Cancer[f]							
All SH cases	2,004	44	2.2	1.14	0.82–1.58	0.93	0.67–1.30
SH with low TSH	1,491	32	2.1	1.12	0.77–1.62	0.90	0.61–1.33
SH with suppressed TSH	414	9	2.2	1.11	0.57–2.16	0.94	0.48–1.84
Comparators	10,111	184	1.8	1.00		1.00	

SH, Subclinical hyperthyroidism.

[a] Significant differences between the three groups (SH with low TSH, SH with suppressed TSH, and controls) and two groups (all SH cases and controls) ($P < 0.05$).

[b] Adjusted for history of cardiovascular disease, history of cerebrovascular disease, history of renal failure, socioeconomic status, diabetic status, and age × gender interaction.

[c] Adjusted for history of dysrhythmia, history of cerebrovascular disease, history of fracture, diabetic status, and age × gender interaction.

[d] Adjusted for history of cardiovascular disease, history of dysrhythmia, diabetic status, and age × gender interaction.

[e] Adjusted for history of dementia, history of psychiatric, and age × gender interaction.

[f] Adjusted for history of cardiovascular disease, history of cancer, diabetic status, socioeconomic status, and age × gender interaction.

and preexisting dysrhythmia ($P < 0.001$) compared with the reference population.

All subclinical hyperthyroid cases

Table 2 shows the unadjusted and adjusted hazard ratios (HR) for inpatient admissions due to cardiovascular disease, osteoporotic fractures, dysrhythmia, dementia, and cancer. In total, there were 1267 episodes of nonfatal cardiovascular disease, 684 of osteoporotic fracture, 256 of dysrhythmia, 204 of dementia, and 228 of cancer. Compared with the reference population, subclinical hyperthyroid patients were associated with an increased risk of cardiovascular morbidity, osteoporotic fracture, dysrhythmia, and dementia. There were no significant differences in the risk of cancer between subclinical hyperthyroid patients and the matched reference population. The presence of diabetes was associated with an increased risk of cardiovascular morbidity [HR = 1.88; 95% confidence interval (CI) = 1.63–2.15], dysrhythmia admissions (HR = 2.22; 95% CI = 1.65–2.97), and cancer admissions (HR = 1.89; 95% CI = 1.35–2.58).

When the subclinical hyperthyroid patients were grouped into two categories based on their TSH measurements for 6 months from baseline, those in group 1 (TSH 0.1–0.4 mU/liter) and those in group 2 (TSH < 0.1 mU/liter) had significantly increased risk of cardiovascular morbidity compared with the reference population; however, the risk was higher among those in group 2. Similarly, those in groups 1 and 2 had increased risk of dysrhythmia, but the risk was higher among those in group 2. Those in group 1 had significantly increased risk of osteoporotic fracture and dementia, whereas the risk of those in group 2 was only marginally increased compared with the reference population. Again, there were no significant differences in risk of cancer between patients in both groups and the reference population. Figure 1 shows Kaplan-Meier curves for each outcome stratified by patient groups.

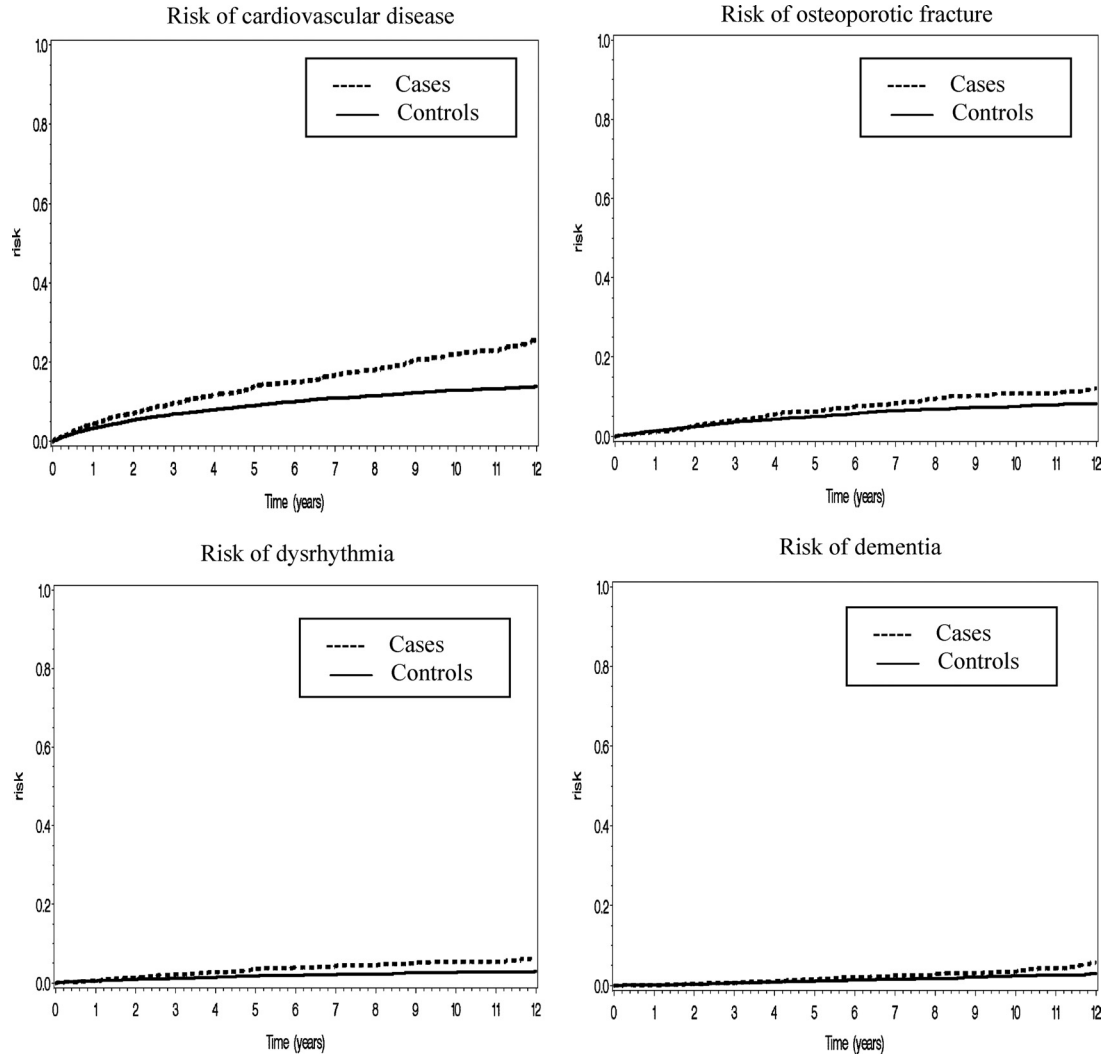

FIG. 1. Kaplan-Meier survival curve showing the risk of cardiovascular disease, osteoporotic fracture, dysrhythmia, and dementia in subclinical hyperthyroid patients. Subclinical hyperthyroid patients had significantly increased risk of cardiovascular disease ($P < 0.001$), osteoporotic fracture ($P < 0.001$), dysrhythmia ($P < 0.001$), and dementia ($P = 0.001$) but not cancer ($P = 0.44$).

Subclinical hyperthyroid cases that remained subclinical

The long-term outcomes of subclinical hyperthyroid patients who remained as subclinical during the study period were investigated (Table 3). Subclinical hyperthyroid patients were associated with an increased risk of cardiovascular morbidity, dysrhythmia. and dementia. There were no significant differences in risk of osteoporotic fractures and cancer between subclinical hyperthyroid patients and the matched reference population.

When the patients were divided into two groups, those in group 1 (TSH = 0.1–0.4 mU/liter) and those in group 2 (TSH < 0.1 mU/liter) had significantly increased risk of cardiovascular morbidity compared with the reference population. Those in group 1 had significantly increased risk of osteoporotic fracture, dysrhythmia, and dementia, whereas the risk of those in group 2 was not significantly different compared with the reference population. There were no significant differences in risk of cancer between patients in both groups and the reference population (Table 3).

Predictive model for cardiovascular disease

A predictive risk model for cardiovascular disease after 5 yr of diagnosis of subclinical hyperthyroidism was developed because the results showed a strong association between subclinical hyperthyroidism and nonfatal cardiovascular morbidity. A predictive model was developed for the cases, and the following variables were identified as significant predictors of nonfatal cardiovascular event: age, gender, SIMD, diabetes, and history of cardiovascular disease, cerebrovascular disease, and renal failure. TSH and FT_4 concentrations at baseline did not predict cardiovascular morbidity in this model. The AUROC curve obtained from this model was 0.74 (95% CI = 0.73–0.76), which reflects moderate to good predictability.

TABLE 3. Unadjusted and adjusted HR for inpatient admissions for cardiovascular, osteoporotic fracture, dysrhythmia, dementia, and cancer for subclinical hyperthyroid patients who remained subclinical throughout the study

		Events		Unadjusted		Adjusted	
	Population	n	%	HR	95% CI	HR	95% CI
Nonfatal cardiovascular[b]							
All SH cases	1,353	202	14.9	1.70[a]	1.46–1.98	1.36[a]	1.17–1.59
SH with low TSH	1,056	158	15.0	1.68[a]	1.42–1.99	1.35[a]	1.13–1.60
SH with suppressed TSH	236	38	16.1	1.90[a]	1.37–2.62	1.58[a]	1.14–2.19
Comparators	10,081	926	9.2	1.00		1.00	
Osteoporotic fracture[c]							
All SH cases	1,353	95	7.0	1.39[a]	1.12–1.73	1.19	0.96–1.49
SH with low TSH	1,056	79	7.5	1.47[a]	1.16–1.86	1.30[a]	1.03–1.65
SH with suppressed TSH	236	14	5.9	1.20	0.70–2.03	0.90	0.53–1.53
Comparators	10,081	527	5.2	1.00		1.00	
Dysrhythmias[d]							
All SH cases	1,353	44	3.3	1.95[a]	1.40–2.72	1.50[a]	1.07–2.09
SH with low TSH	1,056	36	3.4	2.02[a]	1.41–2.89	1.55[a]	1.07–2.23
SH with suppressed TSH	236	5	2.1	1.31	0.54–3.19	1.01	0.42–2.47
Comparators	10,081	174	1.7	1.00		1.00	
Dementia[e]							
All SH cases	1,353	36	2.7	1.96[a]	1.36–2.82	1.95[a]	1.35–2.82
SH with low TSH	1,056	29	2.7	2.01[a]	1.35–2.99	2.03[a]	1.36–3.03
SH with suppressed TSH	236	6	2.5	1.84	0.81–4.15	1.74	0.77–3.96
Comparators	10,081	150	1.5	1.00		1.00	
Cancer[f]							
All SH cases	1,353	30	2.2	1.26	0.86–1.85	0.98	0.66–1.46
SH with low TSH	1,056	25	2.4	1.33	0.88–2.02	1.03	0.67–1.59
SH with suppressed TSH	236	4	1.7	0.99	0.37–2.66	0.82	0.30–2.20
Comparators	10,081	182	1.8	1.00		1.00	

SH, Subclinical hyperthyroidism.

[a] Significant differences between the three groups (SH with low TSH, SH with suppressed TSH, and controls) and two groups (all SH cases and controls) ($P < 0.05$).

[b] Adjusted for history of cardiovascular disease, history of cerebrovascular disease, history of renal failure, socioeconomic status, diabetic status, and age × gender interaction.

[c] Adjusted for history of dysrhythmia, history of cerebrovascular disease, history of fracture, diabetic status, and age × gender interaction.

[d] Adjusted for history of cardiovascular disease, history of dysrhythmia, diabetic status, and age × gender interaction.

[e] Adjusted for history of dementia, history of psychiatric, and age × gender interaction.

[f] Adjusted for history of cardiovascular disease, history of cancer, diabetic status, socioeconomic status, and age × gender interaction.

Discussion

This was a large population-based study that included all patients in Tayside who had at least two TSH measurements below the reference range (≤0.4 mU/liter) with normal FT_4/T_4 and T_3 measurements for at least 4 months. There was an association between subclinical hyperthyroidism and increased risk of cardiovascular disease and dysrhythmia, and possibly fracture and dementia, but not with cancer. After excluding patients who developed hyperthyroidism and those who reverted to normal during the follow-up period, subclinical hyperthyroidism was still associated with an increased risk of cardiovascular disease and dysrhythmia, and possibly dementia, but not with osteoporotic fracture or cancer.

These results are consistent with Sawin *et al.* (15) who reported that patients with TSH concentrations of 0.1 mU/liter or less had an increased risk of developing atrial fibrillation even after excluding those who were receiving thyroid hormone therapy. Leese *et al.* (16) demonstrated that patients under the age of 65 yr taking L-T_4 had a higher incidence of ischemic heart disease than the general population. In contrast, Cappola *et al.* (9) reported no association between subclinical hyperthyroidism and atherosclerotic cardiovascular disease or cardiovascular mortality, but Parle *et al.* (6) reported an increase in cardiovascular mortality in patients with subclinical hyperthyroidism. A metaanalysis of five population-based cohort studies demonstrated that for subclinical hyperthyroidism, the relative risk for coronary heart disease was 1.21 (95% CI = 0.88–1.68) and cardiovascular mortality was 1.19 (95% CI = 0.81–1.76) (17). The current results showed an association between subclinical hyperthyroid patients and increased risk of nonfatal cardiovascular disease (HR = 1.39) and dysrhythmia (HR = 1.65), especially in pa-

tients with TSH measurements below 0.1 mU/liter. There appears to be a dose-response effect because the risk increased with decreasing TSH measurement, suggestive of a possible causal association.

The association between subclinical hyperthyroidism and osteoporotic fracture remains controversial. In this study, subclinical hyperthyroid patients were associated with an increased risk of osteoporotic fracture; however, when patients who developed hyperthyroidism and those who reverted to normal during the follow-up were excluded, there was no significant increase in risk of fracture. When the patients were divided into two groups based on their TSH measurement, there was no dose-response effect, suggesting that the association is less likely to be causal. Confounding factors such as menopausal status, which is associated with fracture, may have affected the results of this study, but this information was not available. In this study, the mean age of female patients was 66.7 yr and 61% were over 65 yr. A metaanalysis on 13 cross-sectional studies reported no significant reduction in bone mass during prolonged subclinical hyperthyroidism in premenopausal women (18). Similarly, Földes *et al.* (11) reported that endogenous subclinical hyperthyroidism resulted in a significant decrease in bone mineral density among postmenopausal women but not among premenopausal women. In contrary, Bauer *et al.* (12) reported that low TSH concentrations were not associated with bone loss in older ambulatory women. Leese *et al.* (16) reported no increased fracture risk in L-T_4-treated patients with TSH concentrations lower than 0.05 mIU/liter or in those with TSH concentrations between 0.05 and 4.0 mIU/liter. Murphy and Williams (10) reported that endogenous subclinical hyperthyroidism has no effect on the bone mass density of premenopausal women.

A recent study from Brazil reported a positive association between subclinical hyperthyroidism and dementia in men (19). A Rotterdam study reported that subclinical hyperthyroid patients had more than a 3-fold increased risk of dementia especially in those who were positive for thyroid peroxidase antibodies (20). However, Gussekloo *et al.* (21) failed to show any association between TSH, disability and cognitive function and survival in old age. The current study was consistent with previous studies that identified an association between subclinical hyperthyroidism and dementia. However, there was no relationship with TSH concentration, suggesting the possibility that dementia is causing a lowered serum TSH rather than the reverse. This finding might also be due to the small number of dementia cases (10 cases) among those in group 2 (TSH $<$ 0.1 mU/liter). This is the first study to report a lack of association between subclinical hyperthyroidism and cancer.

The strength of the current study is that the data are from a large and representative population with long-term follow-up, and as such, the findings will have high validity. One important feature of this study is that diagnosis of subclinical hyperthyroidism was made when at least two TSH concentrations were low ($\leq$0.4 mU/liter) for at least 4 months and not with just a single baseline measurement. This was done to ensure that the cases had stable subclinical hyperthyroidism and not in the early stage of developing overt hyperthyroidism and were unlikely to have sick euthyroid syndrome. We also undertook a subanalysis that excluded all patients who developed overt hyperthyroidism and those who reverted to normal during follow-up and were thus able to identify the true effects of pure subclinical hyperthyroidism. Patients with preexisting hyperthyroidism were excluded. Also excluded were patients with exogenous subclinical hyperthyroidism and those with pituitary disorder. A limitation, however, is that this is an observational study. Therefore, the findings could be the result of residual confounding by unknown factors. However, data were adjusted to account for age, gender, social deprivation, presence of diabetes, and history of other morbidities including cancer. Also, the relatively small sample size in group 2 (TSH $<$ 0.1 mU/liter) restricted the power and minimized the precision in this study.

In summary, patients with subclinical hyperthyroidism appear to be associated with an increased risk of cardiovascular disease and dysrhythmia. There is an association with osteoporotic fracture and dementia that is not related to serum TSH concentration and therefore is less likely to be causally related. No association was found between subclinical hyperthyroidism and cancer.

Acknowledgments

Address all correspondence and requests for reprints to: Thenmalar Vadiveloo, Dundee Epidemiology and Biostatistics Unit, Division of Clinical and Population Sciences and Education, MacKenzie Building, Kirsty Semple Way, University of Dundee, Dundee, Scotland, DD2 4BF United Kingdom. E-mail: t.vadiveloo@cpse.dundee.ac.uk.

Disclosure Summary: T.V., L.C., and G.P.L. have nothing to declare. P.T.D. has received funding for research from GlaxoSmithKline, Amgen, and Pfizer.

References

1. **Vadiveloo T, Donnan PT, Cochrane L, Leese GP** 2011 The thyroid epidemiology, audit, and research study (TEARS): the natural history of endogenous subclinical hyperthyroidism. J Clin Endocrinol Metab 96:E1–E8
2. **Canaris GJ, Manowitz NR, Mayor G, Ridgway EC** 2000 The Col-

orado thyroid disease prevalence study. Arch Intern Med 160:526–534
3. **Marqusee E, Haden ST, Utiger RD** 1998 Subclinical thyrotoxicosis. Endocrinol Metab Clin North Am 27:37–49
4. **Wang C, Crapo LM** 1997 The epidemiology of thyroid diseases and implications for screening. Endocrinol Metab Clin North Am 26: 189–218
5. **Boelaert K, Franklyn JA** 2005 Thyroid hormone in health and disease. J Endocrinol 187:1–15
6. **Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA** 2001 Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. Lancet 358:861–865
7. **Bauer DC, Rodondi N, Stone KL, Hillier TA** 2007 Thyroid hormone use, hyperthyroidism and mortality in older women. Am J Med 120:343–349
8. **Walsh JP, Bremner AP, Bulsara MK, O'Leary P, Leedman PJ, Feddema P, Michelangeli V** 2005 Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. Arch Intern Med 165:2467–2472
9. **Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, Tracy RP, Ladenson PW** 2006 Thyroid status, cardiovascular risk, and mortality in older adults. JAMA 295:1033–1041
10. **Murphy E, Williams GR** 2004 The thyroid and the skeleton. Clin Endocrinol (Oxf) 61:285–298
11. **Földes J, Tarján G, Szathmari M, Varga F, Krasznai I, Horvath C** 1993 Bone mineral density in patients with endogenous subclinical hyperthyroidism: is the thyroid status a risk factor for osteoporosis? Clinical Endocrinology 39:521–527
12. **Bauer DC, Nevitt MC, Ettinger B, Stone K** 1997 Low thyrotropin levels are not associated with bone loss in older women: a prospective study. J Clin Endocrinol Metab 82:2931–2936
13. **Flynn RW, Macdonald TM, Jung RT, Morris AD, Leese GP** 2006 Mortality and vascular outcomes in patients treated for thyroid dysfunction. J Clin Endocrinol Metab 91:2159–2164
14. **Flynn RW, MacDonald TM, Morris AD, Jung RT, Leese GP** 2004 The thyroid epidemiology, audit, and research study: thyroid dysfunction in the general population. J Clin Endocrinol Metab 89: 3879–3884
15. **Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, Wilson PW, Benjamin EJ, D'Agostino RB** 1994 Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med 331:1249–1252
16. **Leese GP, Jung RT, Guthrie C, Waugh N, Browning MC** 1992 Morbidity in patients on L-thyroxine: a comparison of those with a normal TSH to those with a suppressed TSH. Clin Endocrinol (Oxf) 37:500–503
17. **Ochs N, Auer R, Bauer DC, Nanchen D, Gussekloo J, Cornuz J, Rodondi N** 2008 Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. Ann Intern Med 148:832–845
18. **Faber J, Galløe AM** 1994 Changes in bone mass during prolonged subclinical hyperthyroidism due to L-thyroxine treatment: a meta-analysis. Eur J Endocrinol 130:350–356
19. **Benseñor IM, Lotufo PA, Menezes PR, Scazufca M** 2010 Subclinical hyperthyroidism and dementia: the Sao Paulo Ageing, Health Study (SPAH). BMC Public Health 10:298
20. **Kalmijn S, Mehta KM, Pols HA, Hofman A, Drexhage HA, Breteler MB** 2000 Subclinical hyperthyroidism and the risk of dementia. The Rotterdam Study. Clin Endocrinol (Oxf) 53:733–737
21. **Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frölich M, Westendorp RG** 2004 Thyroid status, disability and cognitive function, and survival in old age. JAMA 292:2591–2599