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ORIGINAL ARTICLE

Liothyronine use in a 17 year observational population-based study - the tears study

Graham P. Leese*, Enrique Soto-Pedre† and Louise A. Donnelly†

*Department of Endocrinology and Diabetes, Ninewells Hospital and Medical School, University of Dundee and †Division of Cardiovascular & Diabetes Medicine, School Of Medicine, Ninewells Hospital and Medical School, University of Dundee, Dundee, UK

Abstract

Objective To look at adverse outcomes for patients on liothyronine compared to l-thyroxine. Some trials have examined the relative merits of liothyronine but none have looked at adverse outcomes in large numbers.

Study Design An observational study of all patients prescribed thyroid hormone replacement in Tayside Scotland (population 400 000) from 1997 to 2014.

Patients A study group of patients having ever used liothyronine (n = 400) was compared to those who had only used l-thyroxine (n = 33 955). All patients were followed up until end-point, death or leaving Tayside.

Measurements Mortality rates and admissions with cardiovascular disease, atrial fibrillation, fractures, breast cancer and mental diseases were compared. Incident use of bisphosphonates, statins, antidepressants and antipsychotics was compared.

Results Compared to patients only taking l-thyroxine, those using liothyronine had no increased risk of cardiovascular disease [hazard ratio (HR) 1·04; 95% CI 0·70–1·54], atrial fibrillation (HR 0·91: 0·47–1·75), or fractures (HR 0·79: 0·49–1·27) after adjusting for age. There was no difference in the number of prescriptions for bisphosphonates or statins. There was an increased risk of new prescriptions for antipsychotic medication (HR 2·26: 1·64–3·11 $P < 0·0001$) which was proportional to the number of liothyronine prescriptions. There was a non-significant trend towards an increase in breast cancer and new use of antidepressant medications. During follow-up, median TSH was higher for patients on l-thyroxine alone (2·08 *vs* 1·07 mU/L; $P < 0·001$).

Conclusion For patients taking long-term liothyronine we did not identify any additional risk of atrial fibrillation, cardiovascular disease or fractures. There was an increased incident use of antipsychotic medication during follow-up.

Correspondence: Graham Leese, Ward 5, Ninewells Hospital and Medical School, Dundee, DD1 9SY, UK. Tel.: 01382 740471; Fax: 01382 425509; E-mail: grahamleese@nhs.net

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Introduction

Hypothyroidism affects around 5% of the population and the recommended treatment is l-thyroxine.[1,2] Patients usually respond well to treatment with l-thyroxine, and the dose is monitored in response to a combination of patients' symptoms and serum TSH concentrations. However, some patients describe ongoing adverse symptoms despite being on what seem adequate doses of l-thyroxine, even with serum TSH concentrations towards the lower end of the reference range.[3]

The thyroid gland secretes some tri-iodothyronine, and tri-iodothyronine is the main active hormone at cellular level, converted from thyroxine by intracellular deiodinases. Liothyronine is a drug that is identical to the hormone tri-iodothyronine. As a result a number of trials have been conducted assessing the efficacy of combined l-thyroxine with liothyronine therapy, to see if the combination is better than l-thyroxine alone. Of 12 trials, two showed a significant improvement,[4,5] two a minor improvement[3,6] and eight showed no improvement[7–14] in quality of life scores. In seven trials focussing on changes in thyroid related symptoms, no improvements were observed in the combination therapy group[3,7,8,11–13,15] However, it is possible that there is a subgroup of patients who do benefit. Genetic differences determining activity of the deiodinase gene impacting on serum TSH concentrations have been identified in some[16] but not all studies.[17] However, these results give grounds for an as yet unproven hypothesis that there may be subgroups of patients who may metabolise thyroxine differently, and could possibly benefit from combination therapy.

Given a free choice, patients preferred combination therapy in the majority of trials.[4,5,9,11,13] Although these trials had small numbers, this may hint at some improved outcomes that were not identified in more detailed analyses. However, there was no difference in patient preference in the larger trials,[3,8] although serum TSH was higher in the patients taking combination therapy in one of these trials,[8] which may have reduced any potential benefit.

When assessing the risk of combination therapy, one trial showed no difference in bone density[15] but this was only after 6 months treatment, which is too short a time to be confident there is no long-term impact. There are little useful data on cardiovascular end-points. The majority of trials showed no difference in resting heart rate[3,6,7,11,12,14,15] but with others showing a decrease[4,8,13] and one showing an increase.[9]

Meta-analyses concluded that no major benefit or risk could be detected for combined treatment over l-thyroxine alone,[18–21] but there are very little useful data on the risk of liothyronine. There is a consensus that more long-term data are required to assess the benefits and risks of combination therapy, and although guidelines do allow the provision of combined therapy, they do not recommend its routine use.[1,2] Using linked electronic medical records we aimed to address any potential adverse impact of long-term liothyronine use, either alone or in combination with l-thyroxine in an observational follow-up study.

Materials and methods

A population-based retrospective cohort study was done among patients ever registered with a general practitioner in Tayside; a well-defined geographical region within Scotland (UK) with a population of over 400 000 people, who are mainly Caucasian. All patients are issued a unique patient identification number (Community Health Index -CHI) which facilitates the linkage of all electronic medical records. Data sets described below were linked anonymously by the Health Informatics Centre of the University of Dundee as previously described[22] using the CHI number.

The demographic database provided information on gender, date of birth, patient movement out of Tayside, and deprivation based on each patient's full postcode (Scottish Index of Multiple Deprivation- SIMD). Death of any patient was established throughout the General Registrar Office (GRO) records. The biochemistry database provided serum concentrations of thyroid-stimulating hormone (TSH). The Scottish Care Information-Diabetes Collaboration (SCI Diabetes) database was used to identify all people registered with diabetes in Tayside, and the Scottish Morbidity Records (SMR) to obtain hospital admissions data held by the Information Services Division of the National Health Service (NHS). Any prescription of interest (Table 1) was extracted from the database of prescriptions dispensed from all community pharmacies in Tayside. Anti-arrhythmic drugs were not included as many of the commonly used ones are used for other indications e.g. hypertension, and were therefore not useful as disease specific markers. The International Classification of Diseases (ICD) ninth and 10th revision codes and the Office of Populations Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS-4) codes were used in the SMR to classify all hospital inpatient events and operations (Table 1).

Patients on thyroid hormone therapy were defined as having been issued at least three prescriptions for thyroid replacement therapy during the follow-up period. Baseline data (i.e. prior to starting thyroid replacement therapy) were collected on all patients. The numbers of patients with defined conditions before and after starting the study drug were also collected. The period of follow-up for the analysis was defined from January 1997 to March 2014. For each individual, the date of entry into the study was the first date of thyroid replacement therapy prescription. Each eligible patient was followed from the date of entry until either occurrence of outcome of interest or end of study (i.e. moving out of health area, death or 31 March 2014).

To ensure data quality, SMR data go routinely through a set of validation rules by the Information Services Division (ISD-NHS National Services Scotland). These validation rules check on the validity and feasibility of the data.[23] Besides, ISD carry out periodical data quality assurance exercises to evaluate and ensure SMR data sets are accurate, consistent and comparable across time and between sources.[24]

Table 1. Codes used to identify hospital admissions, operations and prescriptions of interest

Description		
Admissions (SMR)	ICD-9 codes	ICD-10 codes
Thyroid cancer	193	C73, D093, D440
Bone fractures	800-829, E887, M484	M80, M81, S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12, T142
Atrial fibrillation	427·3	I48
Cardiovascular disease	410-429	I20-I25, I44, I45, I47-I50
Breast cancer	174, 175, 198·91, 233·0, 238·3, 239·3	C50, D05
Mental disorders	295-316	F20-F69
Operations (SMR)	OPCS-4 codes	
Thyroid surgery	B08, B09, B12	
Prescriptions	BNF codes	
Thyroid replacement	6·2·1	
Anti-thyroid drugs	6·2·2	
Bisphosphonates	6·6·2	
Antipsychotics	4·2·1, 4·2·2, 4·2·3	
Antidepressants	4·3·1, 4·3·3	
Statins	within section 2·12	

SMR, Scottish Morbidity Records; ICD, International Classification of Diseases (ICD-9, Ninth Revision codes, ICD-10, Tenth Revision codes); OPCS-4, Office of Populations Censuses and Surveys Classification of Surgical Operations and Procedures; BNF, British National Formulary.

Statistical methods

Logic checks were performed and frequency distributions for all variables were analysed for out-of-range values. The mean and standard deviation (SD) of the data were given to describe continuous variables. ANOVA and chi-square tests were used to compare means and frequencies among subgroups of patients, respectively. Statistical significance at $P < 0{\cdot}01$ was chosen *a priori* due to the large number of outcomes being analysed. Survival analysis was performed to follow-up patients and Cox

proportional hazards models were used to explore the relationship between liothyronine use and outcomes. A separate analysis estimating the hazard ratios (HR) with 95% confidence intervals (CI) associated with liothyronine use was performed for each of the outcomes. Univariate and multivariate analyses were performed. Log-rank test of equality across strata were obtained for all categorical covariates, and univariate Cox models were fitted for the continuous covariates to explore whether or not to include them in the multivariate model. A covariate was also considered for inclusion if the univariate test had a p-value $\leq 0{\cdot}2$.[25] Categorical covariates were included as dummy variables and interactions between covariates were also considered for inclusion. A test of the proportional hazards was performed for each covariate and globally using a formal significance test based on the unscaled and scaled Schoenfeld residuals.[26] The sensitivity for model specifications was evaluated using goodness of fit diagnostics by plotting Nelson-Aalen cumulative hazard function for Cox-Snell residuals.[27]

All patients on thyroid replacement therapy were classified into two exposure groups: a) study group-ever exposed to liothyronine, either alone or in combination with thyroxine and b) comparator group-patients on thyroxine who had never received liothyronine. Exposure was coded as binary (i.e. ever *vs* never liothyronine). The proportion of liothyronine prescriptions of all thyroid replacement prescriptions was used to evaluate the effect of liothyronine use and coded as dummy variable.

Sensitivity analyses comprised a Mantel-Haenszel combined incidence risk ratio analysis to explore the relationship between liothyronine use and outcomes. To rule out potential biases, morbidity data analysis was repeated after excluding patients with a prior history of thyroid cancer, and drug data analysis was also repeated after excluding patients possibly treated with thyroid medications for depression.

Outcomes

All outcomes were incident and coded as binary. Patients with prevalent outcomes at baseline were excluded from the survival analysis for that particular outcome. Outcomes were death, newly diagnosed diabetes mellitus, fractures, atrial fibrillation, nonfatal cardiovascular disease, breast cancer, mental disorders, starting prescriptions for bisphosphonates, antipsychotics, antidepressants or statins. Limiting this study to only incident outcomes avoided bias from missing data on prior exposure (i.e. left censoring).[28] Clinical outcomes within the first 6 months and drug prescriptions within the first month of follow-up were excluded from the Multivariate Cox regression models to minimize misclassification.[29]

We evaluated the effects of exposure by including in all models gender, age at baseline and total number of thyroid replacement prescriptions received as strata, and terms for ever-exposure, history of probable hyperthyroidism (defined as previous thyroid surgery, radioactive iodine use and/or anti-thyroid drug use) and history of thyroid cancer. For some outcomes being modelled (see Table 3 and 4 for specifics), the following terms were considered for inclusion: baseline average serum TSH, average baseline serum total cholesterol, history of medication used, nonfatal cardiovascular disease, diabetes mellitus, fractures at any site, mental disorders and SIMD.

Ethical approval

All analyses were performed on anonymized data sets. The study was approved by the Tayside Medical Ethics Committee and data protection by the Tayside Caldicott Guardians. The funders had no role in design, analysis, interpretation or writing of the manuscript.

Results

We identified 34 355 patients as being eligible for the study cohort of which 33 955 received l-thyroxine only (i.e. had never received liothyronine). Overall 400 patients received prescriptions for liothyronine, 327 received liothyronine in combination with l-thyroxine, and 73 had received liothyronine only. The total follow-up was 280 334 person-years with a mean follow-up of 9·3 years (SD 5·6) and a maximum follow-up of 17·3 years. Median (interquartile range) duration of therapy on liothyronine was 10·9 (10·7) years, and median duration on l-thyroxine alone was 8·3 (10·8) years.

Baseline characteristics

Patients on liothyronine (the study group) were younger (mean age 46·8 years) than patients only prescribed l-thyroxine (the comparator group; mean age 59·5 years $P < 0{\cdot}001$)), and thus all data were adjusted for age. SIMD and serum TSH values were available for 96% and 92% of the study subjects, respectively (See Table 2). Serum cholesterol was unavailable for about one-third of the study subjects, who were therefore assigned the mean values. Mean serum TSH was not different between the two groups at diagnostic baseline (14·1 mU/l $\pm$ 27·7 and 11·8 mU/l $\pm$ 19·3). Patients who had taken liothyronine were more likely to have diabetes, a history of thyroid cancer or thyroid surgery, been treated with radioactive iodine, and been prescribed antipsychotic or antidepressant medication than patients only given thyroxine, but were less likely to have cardiovascular disease or be prescribed a statin.

Morbidity and mortality data

Table 3 shows the unadjusted and adjusted HR for all cause mortality and incident inpatient admissions for the primary outcomes. There was no difference in mortality or incidence of fracture, atrial fibrillation, non-fatal cardiovascular disease or diabetes mellitus between the study group and comparator group after adjusting for age, gender and other baseline confounding variables. There was a non-significant trend towards an increased risk of breast cancer in patients taking liothyronine ($P = 0{\cdot}041$). All results were similar in a sub-analysis after excluding all patients with a history of thyroid cancer ($n = 174$ - data not shown). There was a non-significant association between the

Table 2. Description of patients prior to starting thyroid replacement therapy

Characteristic	Thyroid replacement therapy		
	Liothyronine use (n = 400)	Thyroxine only (n = 33 955)	P
n (%)			
Gender (female)	337 (84·3)	27 394 (80·7)	=0·066
SIMD quintile			
1 (most deprived)	58 (15·1)	5172 (15·8)	
2	55 (14·4)	5243 (16·0)	
3	62 (16·2)	5970 (18·2)	
4	132 (34·5)	10 457 (31·9)	
5 (most affluent)	76 (19·8)	5894 (18·0)	=0·543
Diabetes mellitus	14 (3·5)	2467 (7·3)	=0·004
Thyroid cancer	87 (21·8)	121 (0·4)	<0·001
Thyroid surgery	39 (9·8)	52 (0·2)	<0·001
Bone fractures	5 (1·3)	744 (2·2)	=0·297
Atrial fibrillation	2 (0·5)	513 (1·5)	=0·141
Non-fatal cardiovascular disease	6 (1·5)	1329 (3·9)	=0·009
Breast cancer	5 (1·3)	626 (1·8)	=0·570
Mental disorder	2 (0·5)	118 (0·4)	=0·408
Medication use			
Radioactive iodine	38 (9·5)	980 (2·9)	<0·001
Anti-thyroid	25 (6·3)	1472 (4·3)	=0·062
Bisphosphonate	6 (1·5)	790 (2·3)	=0·275
Antipsychotic	40 (10·0)	1480 (4·4)	<0·001
Antidepressant	121 (30·3)	7224 (21·3)	<0·001
Statin	18 (4·5)	4061 (12·0)	<0·001
HRT	54 (13·4)	3531 (10·4)	=0·044
Mean (SD)			
Age (years)*	47·7 (14·1)	59·5 (17·2)	<0·001
Serum TSH (mU/l)†	14·1 (27·7)	11·8 (19·3)	=0·030
Serum cholesterol (mmol/l)	5·3 (1·1)	5·6 (1·2)	=0·026

HRT, Oestrogen containing hormone replacement therapy; SIMD, Scottish Index of Multiple Deprivation; TSH, Thyroid-stimulating hormone.
*Age at first prescription of thyroid replacement therapy.
†Maximum level reached prior to starting on replacement therapy.

proportion of prescriptions for liothyronine received over the duration of follow-up and risk of breast cancer as shown in Fig. 1.

Median TSH concentration during follow-up was greater for patients never taking liothyronine (2·08 mU/l, Interquartile range: 1·07-3·18) compared to any user of liothyronine (1·07 mU/l, IQR; 0·27–2·14; $P < 0·001$), which remained when thyroid cancer patients were removed from the analysis (2·08 mU/l, IQR: 1·08–3·19 *vs* 1·35 mU/l, IQR; 0·5–2·4; $P < 0·001$).

Drug data

Table 4 shows the unadjusted and adjusted HR for new prescriptions of various medications. Data shows that there was a 2·3-fold increased use of new prescriptions for antipsychotics for patients taking liothyronine. There was no increased use of bisphosphonates or statins, and there was a non-significant trend towards increased use of antidepressants ($P = 0·047$ for all users). The number of prescriptions for liothyronine was related to the risk of requiring a new prescription for antipsychotic drugs (Fig. 2), but this association between number of liothyronine prescriptions and outcome was not evident for use of antidepressants. The number of prescriptions of liothyronine showed a strong positive linear relationship with length of exposure (r = 0·79, $P < 0·001$), indicating that the more prescriptions a patient received the longer time they were receiving the drug, and that duration on drug is likely to correlate with the incident prescriptions for antipsychotics.

Some psychiatrists prescribe liothyronine as an antidepressant independent of thyroid disease.[30] We thus performed a sub-analysis only including patients who had documentation of a raised serum TSH (greater than 4 mU/l) sometime during the study period, to try and exclude patients being prescribed liothyronine for non-thyroid reasons. In this subgroup, compared to non-users of liothyronine, HR for first time use of antipsychotics in patients using liothyronine was 1·87 (1·28–2·74; $P = 0·001$). In the same subgroup, compared to non-users of liothyronine, the hazards ratio of antidepressant use in patients using liothyronine was 1·15 (0·93–1·42; $P = 0·18$). All sensitivity analyses confirmed the results of the primary analysis.

Discussion

This is the first study that has addressed issues of the long-term safety of liothyronine therapy in routine clinical practice, as far as we are aware. In 400 patients treated with liothyronine for up to 17 years of follow-up, we could not demonstrate any increased risk of death, fractures, atrial fibrillation, diabetes or cardiovascular disease when compared to 34 000 patients treated with l-thyroxine after adjustment for age and other baseline confounding variables. However there was an increased risk of being prescribed antipsychotic medication ($P < 0·001$). There was also a possible concern about an increased risk of breast cancer and use of antidepressants ($0·01 < P < 0·05$). Patients being prescribed liothyronine were younger, more likely to have previous thyroid cancer, hyperthyroidism (judged by an increased prior use of radioactive iodine and thyroid surgery), had lower TSH during follow-up and were more likely to have previously been prescribed antipsychotics or antidepressants before starting liothyronine. Other differences observed in baseline characteristics are likely to be as a result of the younger age of patients on liothyronine.

As this was an observational study patients were not randomly allocated to treatments, and there would have been an element of bias and self-selection, especially for use of liothyronine. The number of patients on liothyronine was relatively low at 400, and the results need confirmation in a larger randomised trial. Our study may be under powered to demonstrate any differences, and the mean duration of follow up of 9 years may not have been long enough to demonstrate any adverse outcomes. In addition there may be subgroups of patients who do particularly poorly

Table 3. Estimates of hazard ratios for different thyroid replacement therapies on having several outcomes

Outcome	Population at risk	Events n (%)	Unadjusted		Adjusted	
			HR	95%CI	HR	95%CI
Bone fractures*						
Never T3	32 654	3015 (9·2)	1·000	–	1·00	–
Ever used T3	393	20 (5·0)	0·439	0·283–0·682	0·792	0·493–1·272
Atrial fibrillation†						
Never T3	32 914	1694 (5·1)	1·000	–	1·00	–
Ever T3 (all T3 users)	398	11 (2·7)	0·449	0·248–0·813	0·911	0·473–1·754
Non-fatal cardiovascular disease‡						
Never T3	31 986	3898 (12·2)	1·000	–	1·00	–
Ever used T3	392	30 (7·6)	0·531	0·371–0·761	1·040	0·703–1·538
Breast cancer§						
Never T3	32 864	740 (2·2)	1·000	–	1·00	–
Ever used T3	395	15 (3·7)	1·419	0·851–2·367	1·754	1·024–3·006 (P = 0·041)
Diabetes mellitus						
Never T3	30 954	2358 (7·6)	1·000	–	1·00	–
Ever used T3	386	23 (5·9)	0·358	0·436–0·992	0·828	0·406–1·686
Mental disorder¶						
Never T3	33 360	443 (1·3)	1·000	–	1·00	–
Ever used T3	398	9 (2·2)	1·421	0·734–2·749	1·558	0·787–3·083
Death**						
Never T3	33 509	8937 (26·6)	1·000	–	1·00	–
Ever used T3	400	42 (10·5)	0·325	0·240–0·441	0·771	0·541–1·100

HR, Hazard ratio; T3, Liothyronine; T4, Thyroxine; TSH, Thyroid-stimulating hormone. All models were stratified by age, gender and total number of thyroid replacement therapy prescriptions received, and adjusted for baseline TSH concentration and history of probable hyperthyroidism and history of thyroid cancer.

*Adjusted also for history of bisphosphonates use.

†Adjusted also for history of non-fatal cardiovascular disease.

‡Adjusted also for history of diabetes mellitus, and history of statin medication use.

§Adjusted also for history of oestrogen containing hormone replacement therapy use.

¶Adjusted also for history of antidepressant medication use, and history of antipsychotic medication use.

**Adjusted also for history of non-fatal cardiovascular disease, and a Scottish index of multiple deprivation.

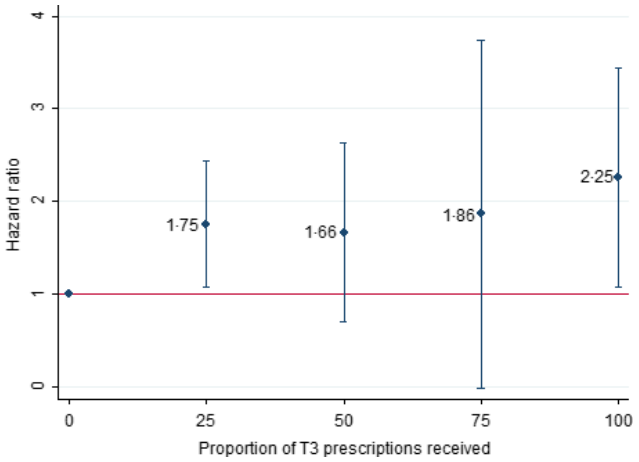

Fig. 1 Estimated hazard ratios (±SE) for breast cancer according to proportion of all thyroid replacement therapy prescriptions being for liothyronine. Hazard ratios calculated using a Cox proportional hazards model adjusted also for history of probable hyperthyroidism, history of thyroid cancer and history of oestrogen containing hormone replacement therapy use. Proportion of T3 (liothyronine) prescriptions received (0, 1–24, 25–49, 50–74 and 75–100 per cent).Wald test for significance of the variable taken as a whole, $\chi^2(4) = 5{\cdot}25$, $P = 0{\cdot}2621$.

that were not identified.There were no obvious trends in any predicted outcomes, except possibly an increased use of bisphosphonates. However, there was no trend towards hospitalized bone fractures, although this would have been a less sensitive outcome. During follow-up, serum TSH was lower in patients taking liothyronine, but it would be expected that this would exaggerate any differences in outcome rather than hide them. Results were adjusted for known potential confounders and there were sizable changes to the risk estimates. The impact of missing values is considered low. There was no information on compliance, but it is thought unlikely that this would introduce a systematic bias. The data on morbidity mainly relates to hospital admission data and would have missed out-patient activity. However, the prescription data included all out-patient prescriptions. Unfortunately there are no useful medications that are exclusively used for atrial fibrillation and thus no surrogate pharmacological marker for atrial fibrillation was measured. It was difficult to exclude patients treated with thyroid medications for depression, but we undertook a sub-analysis where only patients with a raised TSH were included which should have excluded patients treated for depression, and the results remained consistent. Our study however does reflect "real world" clinical practice and followed

Table 4. Estimates of hazard ratios for different thyroid replacement therapies on starting several medications

Start on medication	Population at risk	Events n (%)	Unadjusted		Adjusted	
			HR	95%CI	HR	95%CI
Bisphosphonates†						
Never T3	33 094	3133 (9·4)	1·000	–	1·000	–
Ever used T3	393	31 (7·8)	0·663	0·465–0·944	1·336	0·906–1·971
Antipsychotics‡						
Never T3	32 351	2478 (7·6)	1·000	–	1·000	–
Ever used T3	358	46 (12·8)	1·365	1·020–1·828	2·261	1·642–3·114*
Antidepressants§						
Never T3	26 411	9516 (36·0)	1·000	–	1·000	–
Ever used T3	276	140 (50·7)	1·131	0·957–1·337	1·210	1·002–1·462 (P = 0·047)
Statins¶						
Never T3	29 765	8505 (28·5)	1·000	–	1·000	–
Ever used T3	382	83 (21·7)	0·623	0·502–0·774	0·952	0·645–1·406

HR, Hazard ratio; T3, Liothyronine; T4, Thyroxine; TSH, Thyroid-stimulating hormone; All models were stratified by age, gender and total number of thyroid replacement therapy prescriptions received, and adjusted for average serum TSH at baseline, history of probable hyperthyroidism and history of thyroid cancer.
*Significant at $P < 0·01$.
†Adjusted also for history of bone fractures.
‡Adjusted also for history of antidepressant medication use and history of mental disorders.
§Adjusted also for history of antipsychotic medication use and history of mental disorders.
¶Adjusted also for average serum total cholesterol at baseline, history of non-fatal cardiovascular disease and history of diabetes mellitus.

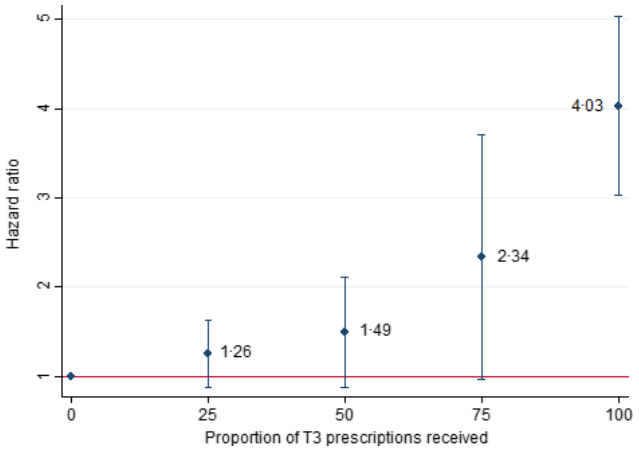

Fig. 2 Estimated hazard ratios (±SE) for antipsychotic medication use according to proportion of all thyroid replacement therapy prescriptions being for liothyronine. Hazard ratios calculated using a Cox proportional hazards model adjusted also for average serum thyroid-stimulating hormone at baseline, history of probable hyperthyroidism, history of thyroid cancer, history of antidepressant medication use and history of mental disorders. Proportion of T3 (liothyronine) prescriptions received (0, 1–24, 25–49, 50–74 and 75–100 per cent). Wald test for significance of the variable taken as a whole, $\chi^2(4) = 33·64$, $P < 0·001$.

patients for a long duration with 280 334 patient-years of follow up.

Patients using liothyronine were more likely to be prescribed antipsychotic agents and antidepressants before starting liothyronine and more likely to be prescribed antipsychotics for the first time after starting liothyronine. In an attempt to remove patients being prescribed liothyronine or thyroxine for depression, a subgroup was analysed comprising only patients who at sometime had a raised serum TSH concentration, and were thus likely to have primary thyroid disease. In this sub-group the association with new prescriptions for antipsychotics remained significant. Overall our data suggest that use of liothyronine increases the risk of being prescribed antipsychotics and possibly other mental health disorders compared to patients using thyroxine for thyroid replacement therapy. Interestingly there was an association between the number of liothyronine prescriptions and use of antipsychotics (Fig. 2), consistent with the association being a direct causal effect of the liothyronine. The number of prescriptions showed a strong positive linear relationship with length of exposure ($r = 0·79$, $P < 0·001$), and the association with antipsychotics remained if length of exposure was used as an alternative to number of prescriptions. There was no clear association with number of liothyronine prescriptions and number of new prescriptions for antidepressants.

The possible association with breast cancer is a concern. In breast cancer cell lines it has been demonstrated that tri-iodothyronine can augment the cell proliferation potential of estrogens, thus possibly increasing the malignant potential in breast cancer cells lines.[31,32] This is supported by a recent trial where higher endogenous serum tri-iodothyronine was associated with breast tumours demonstrating more aggressive characteristics[33] and increased mortality.[34] However, the association with breast cancer was of borderline statistical significance in the overall group and the association was not related to the number

of liothyronine prescriptions, which raises doubt as to whether this association is causally related or not.

The majority of randomized controlled trials show no overall benefit of combined treatment with L-thyroxine and liothyronine compared to L-thyroxine alone, and this conclusion is supported by at least four meta-analyses.[18–21] However, there is a subset of patients who remain dissatisfied with L-thyroxine replacement treatment, and a further subset of these who claim to feel better on combination treatment. Additionally, in randomized trials where a blinded global assessment of preference was studied, in four of five trials the combination treatment was preferred.[18] Thus, despite no clear evidence of benefit of using liothyronine in trials, a proportion of patients are keen to pursue combined therapy. A key question is whether such an approach does any harm to patients, and our data should be useful to inform patients about the risk to benefit ratio of being prescribed liothyronine for hypothyroidism. The population of Tayside is similar to the UK in general, and these results are likely to be of general relevance at least in countries with modern health services. The cost of treatment remains a residual issue for a health-care service as liothyronine is more expensive than thyroxine, although the extent of this varies between countries. Such issues would need to be discussed at a local level.

In conclusion, we could not identify any increased risk of atrial fibrillation, cardiovascular disease, fracture or use of bisphosphonates with the use of liothyronine in this observational study. Such patients did have an increased risk of being prescribed incident antipsychotic medication. There were non-statistical associations with breast cancer and use of antidepressant medication. Further work is required to clarify the relevance of these associations, but the study provides useful initial information on the relative risk to benefit ratio of using liothyronine.

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Conflict of interest

Nothing to declare.

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