Articles

Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study

James V Parle, Patrick Maisonneuve, Michael C Sheppard, Peter Boyle, Jayne A Franklyn

Summary

Background Low serum thyrotropin, in combination with normal concentrations of circulating thyroid hormones, is common, especially in elderly people and in individuals with a history of thyroid disease. We aimed to assess the long-term effects of subclinical hyperthyroidism on mortality.

Methods We did a population-based study of mortality in a cohort of 1191 individuals not on thyroxine or antithyroid medication. All participants were aged 60 years or older. We measured concentration of thyrotropin in serum at baseline in 1988–89. We recorded vital status on June 1, 1999, and ascertained causes of death for those who had died. We compared data for causes of death with age-specific, sex-specific, and year-specific data for England and Wales. We also compared mortality within the cohort according to initial thyrotropin measurement.

Results During 9733 person-years of follow-up, 509 of 1191 people died, the expected number of deaths being 496 (standardised mortality ratio [SMR] 1·0, 95% CI 0·9–1·1). Mortality from all causes was significantly increased at 2 (SMR 2·1), 3 (2·1), 4 (1·7), and 5 (1·8) years after first measurement in those with low serum thyrotropin (n=71). These increases were largely accounted for by significant increases in mortality due to circulatory diseases (SMR 2·1, 2·2, 1·9, 2·0, at years 2, 3, 4, and 5 respectively). Increases in mortality from all causes in years 2–5 were higher in patients with low serum thyrotropin than in the rest of the cohort (hazard ratios for years 2, 3, 4, and 5 were 2·1, 2·2, 1·8, and 1·8, respectively). This result reflects an increase in mortality from circulatory diseases (hazard ratios at years 2, 3, 4, and 5 were 2·3, 2·6, 2·3, 2·3), and specifically from cardiovascular diseases (hazard ratios at years 2, 3, 4, and 5 were 3·3, 3·0, 2·3, 2·2).

Interpretation A single measurement of low serum thyrotropin in individuals aged 60 years or older is associated with increased mortality from all causes, and in particular mortality due to circulatory and cardiovascular diseases.

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Introduction

The widespread availability of sensitive assays for the measurement of thyrotropin in serum has led to recognition that concentrations of serum thyrotropin are often low in patients with apparently normal thyroid function. This knowledge has resulted in the description of a condition termed subclinical hyperthyroidism, which is defined as a reduction in serum thyrotropin in association with normal concentrations of the circulating thyroid hormones thyroxine and tri-iodothyronine.[1] The condition is common in people taking thyroxine replacement therapy, in those with goitre, and after treatment of hyperthyroidism;[2,3] in these situations low serum thyrotropin is thought to suggest mild thyroid hormone excess.

Subclinical hyperthyroidism is common, with estimates of prevalence in iodine-replete areas varying from 3·9% in adults of all ages (thyrotropin ≤0·2 mU/L)[4] to 5·9% in those aged 60 years and older (≤0·5 mU/L);[5] prevalence might be even higher than average in areas of iodine deficiency. Although subclinical hyperthyroidism is common, the clinical importance of these biochemical abnormalities is unclear. There is debate about the potential adverse effect of subclinical hyperthyroidism on bone metabolism and on the cardiovascular system.[1] Results of studies showing a reduction in bone mineral density associated with thyrotropin-suppressive doses of thyroxine[6] have led to concern about later risk of osteoporotic fracture, and effects of thyroxine treatment on indices of cardiovascular function[7,8] have raised doubts about long-term circulatory morbidity and mortality.

Results of a large study[9] of patients aged 60 years and older, forming part of the Framingham population, showed that people with suppressed serum thyrotropin (≤0·1 mU/L) had a relative risk for development of atrial fibrillation of 3·1 (95% CI 1·7–5·5) compared with those with normal serum thyrotropin concentrations, lending support to the view that mild thyroid hormone excess might result in long-term vascular morbidity. That study did not, however, examine the association of concentrations of serum thyrotropin with mortality, and the study population was heterogeneous in that some of those with low serum thyrotropin were taking thyroxine therapy whereas others were not. Our aim was to investigate the relation between serum thyrotropin and mortality from all causes, and due to circulatory diseases in elderly people.

Methods

Participants

We enrolled 1209 individuals who were registered with one primary care practice in Birmingham, UK. We originally recruited people for a study of the prevalence of abnormalities of thyrotropin in a population-based cohort; characteristics of the cohort (table 1) and results are

	Overall	Serum TSH (mU/L)				
		<0·5	0·5–1·2	1·3–2·0	2·1–5·0	>5·0
Men						
Number of participants	510	28	171	165	131	15
Age at baseline (mean [SD]) (years)	70·1 (6·1)	71·3 (6·4)	70·4 (6·0)	69·5 (6·3)	70·1 (5·9)	69·4 (5·7)
Age at baseline (median [range]) (years)	69 (60–90)	70 (63–84)	70 (60–85)	68 (60–90)	69 (60–90)	68 (62–81)
Person-years of observation	3883	180	1240	1356	1006	101
Number of deaths	267	14	99	76	67	11
Women						
Number of participants	681	43	163	195	201	79
Age at baseline (mean [SD]) (years)	70·7 (7·3)	73·1 (7·5)	72·3 (8·0)	70·8 (7·4)	69·4 (6·5)	69·3 (6·5)
Age at baseline (median [range]) (years)	69 (60–94)	72 (61–89)	71 (60–94)	69 (60–91)	68 (60–92)	68 (60–88)
Person-years of observation	5850	325	1364	1665	1769	727
Number of deaths	242	20	62	75	65	20

TSH=thyrotropin.

Table 1: **Demographic characteristics**

described elsewhere.[5] Briefly, all individuals were living in the community at the time of recruitment and were aged 60 years or older on June 1, 1988. We excluded patients who were being prescribed thyroxine or antithyroid medication (n=18). We took a venous blood sample from every person (n=1191) between June 1, 1988, and May 30, 1989, and stored it at –20°C until we did thyrotropin assays. Two investigators (JVP and MCS) clinically assessed the individuals with abnormal thyrotropin results, who were reviewed at yearly intervals with repeat biochemical tests.

Protocol

We measured serum thyrotropin with a Serono MAIA-clone method (Serono Diagnostics, Surrey, UK). During the study, the functional sensitivity of the assay used was 0·1 mU/L. We established the normal range of 0·5–5·0 mU/L from samples taken from 150 healthy volunteers. We further assessed participants with thyrotropin concentrations outside the normal range by measurement of serum concentrations of free thyroxine and free tri-iodothyronine (Amerlex M radioimmunoassay kits, Amersham International, Buckinghamshire, UK). The normal ranges for free thyroxine and free tri-iodothyronine were 9·0–24·0 pmol/L and 2·0–8·0 pmol/L, respectively.[5]

Data analysis

For analysis, we grouped individuals according to their serum thyrotropin concentration (low <0·5 mU/L, normal 0·5–5·0 mU/L, high >5·0 mU/L). We further divided participants with low serum thyrotropin into those with low but detectable thyrotropin (0·1–0·49 mU/L) and those with undetectable thyrotropin (<0·1 mU/L). We also subdivided individuals with normal serum thyrotropin into three tertiles of similar size (thyrotropin 0·5–1·2 mU/L, 1·3–2·0 mU/L, and 2·1–5·0 mU/L). We compared serum concentrations of free thyroxine and free tri-iodothyronine between thyrotropin groups with the Wilcoxon rank sum test.

We set a census date of June 1, 1999, and sent demographic details of those in the cohort, but no longer registered with the primary care practice (ie, dead or moved away, n=661), to the UK Office for National Statistics for tracing on the National Health Service Central Register (national register of deaths). Of this group, we traced and ascertained vital status on June 1, 1999, of 660 individuals. Death certificates were supplied for those who had died, on which reported causes of death were coded by the Office of National Statistics according to the ninth revision of the International Classification of Diseases (ICD9).

We compared the underlying cause of death with age-specific mortality data for England and Wales recorded in the WHO databank. Year-specific data were applied for the years 1988–97 (the most recent year for which data were available), and data from 1997 were applied to the years 1998 and 1999. The number of person-years at risk was calculated from the date of the initial blood sample

Cause of death	Observed deaths, SMR (95% CI)					
	After 1 year	After 2 years	After 3 years	After 4 years	After 5 years	At end of follow-up
All causes						
Total	39, 0·8 (0·6–1·1)	105, 1·1 (0·9–1·3)	155, 1·1 (0·9–1·3)	208, 1·1 (1·0–1·2)	266, 1·1 (1·0–1·3)	509, 1·0 (1·0–1·1)
Men	19, 0·8 (0·5–1·2)	53, 1·1 (0·8–1·4)	80, 1·1 (0·9–1·4)	111, 1·1 (1·0–1·4)	145, 1·2 (1·0–1·4)	267, 1·1 (1·0–1·3)
Women	20, 0·8 (0·5–1·3)	52, 1·1 (0·8–1·5)	75, 1·1 (0·9–1·3)	97, 1·0 (0·8–1·3)	121, 1·0 (0·9–1·2)	242, 0·9 (0·8–1·1)
Thyrotropin						
<0·5 mU/L	1, 0·3 (0·0–2·1)	14, 2·1 (1·2–3·5)	20, 2·1 (1·4–3·3)	21, 1·7 (1·1–2·7)	27, 1·8 (1·3–2·7)	34, 1·2 (0·9–1·7)
0·5–1·2 mU/L	13, 0·9 (0·5–1·5)	34, 1·1 (0·8–1·6)	53, 1.2 (0·9–1·6)	70, 1·2 (0·9–1·5)	87, 1·2 (1·0–1·5)	161, 1·1 (0·9–1·3)
1·3–2·0 mU/L	11, 0·8 (0·4–1·4)	21, 0·7 (0·5–1·1)	35, 0·8 (0·6–1·1)	51, 0·9 (0·7–1·1)	66, 0·9 (0·7–1·1)	151, 1·0 (0·9–1·2)
2·1–5·0 mU/L	13, 1·1 (0·6–1·8)	30, 1·2 (0·9–1·8)	40, 1·1 (0·8–1·5)	56, 1·1 (0·9–1·5)	70, 1·1 (0·9–1·4)	132, 1·0 (0·8–1·2)
>5·0 mU/L	1, 0·4 (0·1–2·5)	6, 1·0 (0·5–2·3)	7, 0·8 (0·4–1·6)	10, 0·8 (0·4–1·5)	16, 1·0 (0·6–1·7)	31, 0·9 (0·6–1·3)
Circulatory diseases						
Total	17, 0·7 (0·5–1·2)	47, 1·0 (0·8–1·4)	62, 0·9 (0·7–1·1)	79, 0·9 (0·7–1·1)	107, 0·9 (0·8–1·1)	208, 0·9 (0·8–1·0)
Men	3, 0·3 (0·1–0·8)	17, 0·7 (0·5–1·2)	22, 0·6 (0·4–1·0)	32, 0·7 (0·5–1·0)	48, 0·8 (0·6–1·1)	104, 1·0 (0·8–1·2)
Women	14, 1·2 (0·7–2·1)	30, 1·3 (0·9–1·9)	40, 1·2 (0·9–1·6)	47, 1·0 (0·8–1·4)	59, 1·0 (0·8–1·3)	104, 0·9 (0·7–1·1)
Thyrotropin						
<0·5 mU/L	0	7, 2·1 (1·0–4·5)	10, 2·2 (1·2–4·0)	11, 1·9 (1·0–3·4)	14, 2·0 (1·2–3·3)	17, 1·3 (0·8–2·0)
0·5–1·2 mU/L	4, 0·5 (0·2–1·4)	12, 0·8 (0·5–1·5)	18, 0·8 (0·5–1·3)	25, 0·9 (0·6–1·3)	31, 0·9 (0·6–1·2)	61, 0·9 (0·7–1·2)
1·3–2·0 mU/L	5, 0·7 (0·3–1·7)	10, 0·7 (0·4–1·3)	12, 0·6 (0·3–1·0)	16, 0·6 (0·3–0·9)	23, 0·7 (0·4–1·0)	55, 0·8 (0·6–1·0)
2·1–5·0 mU/L	7, 1·2 (0·6–2·5)	16, 1·4 (0·8–2·2)	20, 1·1 (0·7–1·7)	25, 1·1 (0·7–1·6)	33, 1·1 (0·8–1·6)	64, 1·0 (0·8–1·3)
>5·0 mU/L	1, 0·7 (0·1–5·2)	2, 0·7 (0·2–2·9)	2, 0·5 (0·1–1·9)	2, 0·3 (0·1–1·4)	6, 0·8 (0·4–1·8)	11, 0·7 (0·4–1·2)

Table 2: **Observed number of deaths and standardised mortality ratios (SMR)**

Cause of death	Hazard ratios (95% CI)					
	After 1 year	After 2 years	After 3 years	After 4 years	After 5 years	At end of follow-up
All causes	0·4 (0·0–2·6)	2·1 (1·2–3·8)	2·2 (1·4–3·5)	1·8 (1·1–2·8)	1·8 (1·2–2·7)	1·2 (0·8–1·7)
Other (ICD-9 code)						
Malignant neoplasms (140–208)	..	2·3 (0·8–6·7)	1·9 (0·8–4·9)	1·4 (0·6–3·5)	1·7 (0·8–3·6)	1·1 (0·5–2·2)
Circulatory diseases (390–459)	..	2·3 (1·0–5·2)	2·6 (1·3–5·2)	2·3 (1·2–4·4)	2·3 (1·3–4·0)	1·4 (0·9–2·4)
Cardiovascular diseases (390–414)	..	3·3 (1·3–8·0)	3·0 (1·3–6·8)	2·3 (1·1–5·2)	2·2 (1·1–4·4)	1·4 (0·8–2·6)
Cerebrovascular diseases (430–438)	..	1·0 (0·1–7·7)	1·8 (0·4–7·9)	2·2 (0·7–7·7)	2·8 (0·9–8·2)	1·8 (0·7–4·7)
Respiratory diseases (460–519)	2·6 (0·3–22·3)	1·6 (0·4–7·1)	2·8 (1·0–8·1)	2·2 (0·8–6·4)	1·7 (0·6–4·7)	1·1 (0·5–2·6)

Table 3: **Risk of death for individuals with a serum thyrotropin concentration <0·5 mU/L compared with those with a concentration of ⩾0·5 mU/L**

until June 1, 1999, or date of death. We calculated the expected number of deaths by multiplying the number of person-years in each stratum, defined according to age, sex, and calendar year, by the corresponding mortality rate for that age, sex, and period in England and Wales. We used the standardised mortality ratio (SMR; the ratio of observed to expected deaths) as the estimate of relative risk, and calculated 95% CI for the SMR on the assumption that the observed number of deaths followed a Poisson distribution.

We produced Kaplan-Meier curves to compare survival of patients according to their serum thyrotropin concentration at recruitment. Cox's proportional hazards regression was used to assess the prognostic importance of a low serum thyrotropin measurement after adjustment for age and sex. We used the hazard ratios with 95% CI to estimate the adjusted relative risk of dying for individuals with low thyrotropin values compared with the rest of the cohort. The relative risk associated with a low serum thyrotropin concentration at initial measurement was calculated at 1, 2, 3, 4, and 5 years after initial measurement, and at the end of the study (about 10 years). We analysed data with SAS (version 6.08). All significance tests were two-sided.

Results

Of 1191 individuals, 71 (6%) had serum thyrotropin concentrations below the normal range (including 20 with undetectable serum thyrotropin of <0·1 mU/L) and 94 (8%) above the normal range (table 1). Of those with abnormal thyrotropin concentrations, one had overt hyperthyroidism (low thyrotropin and high free thyroxine) and was put on antithyroid medication at the start of the study, and 18 had overt hypothyroidism (high thyrotropin and low free thyroxine) and began thyroxine replacement therapy at the start of the study. Of the 70 individuals with subclinical hyperthyroidism, 25 (34%) had thyroid enlargement on clinical examination; none of the 70 had other clinical features of thyroid disease. 69 patients were in sinus rhythm and one had atrial fibrillation at the time of blood sampling. During follow-up, three patients (with initial thyrotropin concentrations of 0·05, 0·05, and 0·35 mU/L, respectively) developed overt hyperthyroidism 2, 3, and 4 years after initial blood sampling, none of whom died before June 1, 1999. Of the 76 with subclinical hypothyroidism, 20 (26%) had thyroid enlargement at recruitment. All these patients were in sinus rhythm. 30 (40%) individuals with subclinical hypothyroidism developed overt hypothyroidism and began thyroxine replacement treatment during follow-up.

The minimum time between blood sampling and the census date for the study was 10 years; because some patients died before the census date, the mean duration of follow-up was 8·2 (SD 3·3) years, with 9733 person-years of observation. During follow-up, 509 of 1191 patients died, a number very close to the expected one of 496, calculated from age-specific, sex-specific, and calendar year-specific death rates for England and Wales (SMR 1·0, 95% CI 0·9–1·1). Likewise, mortality in those with normal serum thyrotropin (when considered together and when divided according to thyrotropin tertiles) and in those with raised concentrations did not differ significantly from expected numbers derived from data for England and Wales (table 2). By contrast, assessment of mortality from all causes in those with low serum thyrotropin revealed significant differences from expected findings when analysed at 2, 3, 4, and 5 years after first measurement (table 2). Closely similar increases in mortality due to circulatory diseases were seen in the low thyrotropin group at these times (table 2).

Comparison within the cohort of those with a low serum thyrotropin concentration at initial measurement with the rest of the patients revealed significant increases in mortality from all causes, from circulatory diseases in general, and specifically from cardiovascular diseases (table 3). We did not observe a similar difference in deaths due to other major causes (malignant neoplasms and respiratory diseases) in those with low serum thyrotropin (table 3). Comparison of mortality in those with high serum thyrotropin and normal serum thyrotropin revealed no significant difference.

Figure 1 shows the association between serum thyrotropin concentrations at the start of the study and survival. A difference in survival between groups was evident; poorest survival was seen in those with low serum thyrotropin concentrations. We showed no difference in survival between those with low but detectable thyrotropin

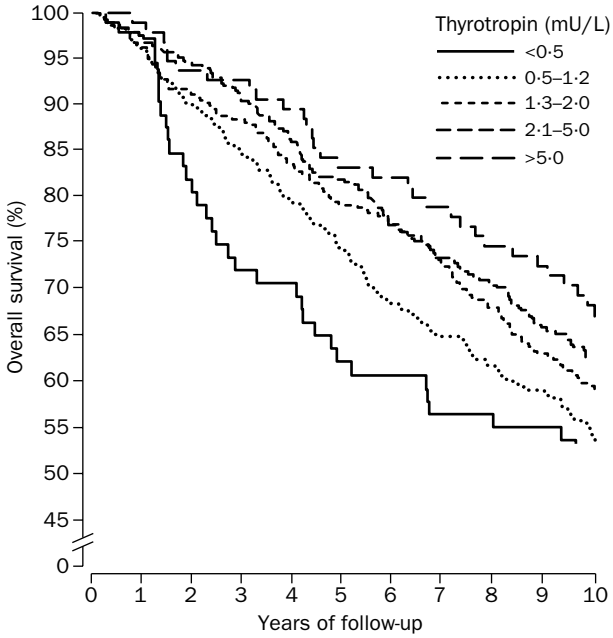

Figure 1: **Kaplan-Meier survival curves showing the relation between overall survival and serum thyrotropin concentration**

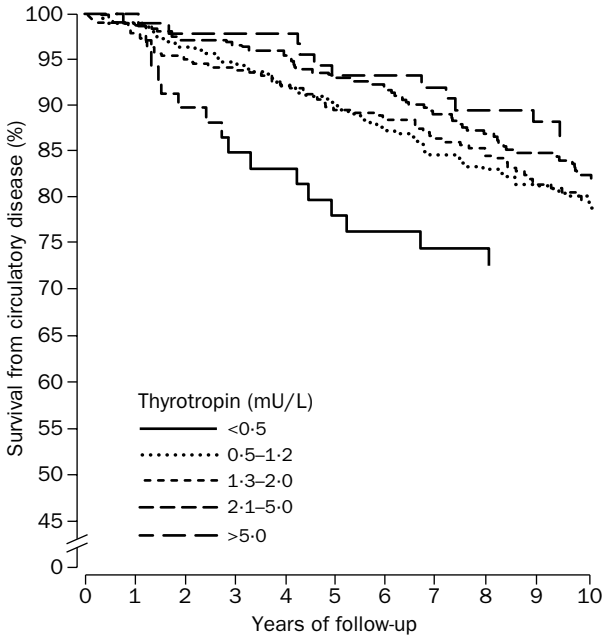

Figure 2: **Kaplan-Meier survival curves showing the relation between survival from circulatory disease and serum thyrotropin concentration**

(0·1–0·49 mU/L, n=51) and those with undetectable thyrotropin (<0·1 mU/L, n=20) (data not shown). Figure 2 shows the association between serum thyrotropin concentrations and survival from circulatory diseases. Poorest survival from circulatory diseases was seen in those with low serum thyrotropin. Analysis of men and women separately did not affect results.

Among those with low concentrations of serum thyrotropin at first measurement, there were significant correlations between serum thyrotropin and free thyroxine ($r=-0·33$, p=0·005) and free tri-iodothyronine ($r=-0·40$, p<0·001). Mean serum free thyroxine and free tri-iodothyronine (measured in those with abnormal thyrotropin) were significantly higher in individuals with low than in those with high thyrotropin values (free thyroxine 15·9 [SD 3·5] pmol/L *vs* 10·5 [2·8] pmol/L, p<0·001; free tri-iodothyronine 5·8 [1·4] pmol/L *vs* 4·8 [1·0] pmol/L, p<0·001). Mean serum free thyroxine and tri-iodothyronine concentrations were also higher in those with undetectable thyrotropin than in those with low but detectable thyrotropin (free thyroxine 17·5 [3·9] pmol/L *vs* 15·2 [3·2] pmol/L, p=0·032; free tri-iodothyronine 6·9 [1·4] pmol/L *vs* 5·3 [1·1] pmol/L, p<0·001). Significant associations between serum concentrations of free thyroxine or free tri-iodothyronine and mortality due to all causes, or to circulatory diseases, were not seen.

Discussion

Our results show an increase in mortality from all causes and from circulatory diseases in individuals with subclinical hyperthyroidism. Patients with a low serum thyrotropin at the start of our study were at a clear survival disadvantage during the first 5 years of follow-up. Significant increases in mortality in individuals with low thyrotropin at the start of the study were no longer present at the end of follow-up, however. This finding is expected, since whatever the initial concentration of thyrotropin, everyone will eventually die.

Our results show that a single low serum thyrotropin concentration in a population-based cohort predicts increased all-cause mortality and circulatory mortality. This finding complements that of Sawin and colleagues,[9] who reported a pronounced increase in frequency of atrial fibrillation in individuals with low serum concentrations of thyrotropin, atrial fibrillation being a known independent risk factor for vascular events. In accordance with their results, we did not record an association between serum free thyroxine or free tri-iodothyronine concentrations and mortality in participants with low serum thyrotropin, suggesting the greater specificity of measurement of serum thyrotropin as a tissue marker of thyroid status.

We believe that a reduction in serum thyrotropin indicates mild thyroid hormone excess in our population-based cohort of elderly people, since (1) the mean concentration of serum free thyroid hormones differed between the groups divided according to serum thyrotropin concentrations; (2) there was an inverse association between serum thyrotropin and free thyroxine (and free tri-iodothyronine) concentrations; and (3) more than a third of individuals with low serum thyrotropin had clinical evidence of thyroid enlargement. However, reduction in serum thyrotropin might also reflect other factors such as non-thyroidal illness.[1,2]

Few other studies have investigated the relation between serum thyrotropin as a marker of mild hyperthyroidism and cardiovascular events or mortality. Leese and colleagues,[10] investigated 1180 patients taking thyroxine replacement therapy in Scotland. They reported an increase in the number of hospital admissions due to ischaemic heart disease among those aged 65 years and older compared with the general population, but no difference in hospital admission rates between those with low serum thyrotropin concentrations secondary to thyroxine treatment (who made up 59% of the cohort) compared with those with normal serum thyrotropin concentrations. Unlike Sawin[9] and Leese and their co-workers,[10] we specifically excluded individuals taking thyroxine replacement at the time of recruitment. In our cohort, low serum thyrotropin might be a better marker of thyroid hormone excess than in those taking thyroxine, since thyrotropin is likely to indicate endogenous overproduction of both thyroxine and tri-iodothyronine.

Overt hyperthyroidism has an adverse effect on the cardiovascular system,[11,12] symptoms and signs being especially prominent in elderly people. We have previously reported a large excess of both cardiovascular and cerebrovascular mortality in patients of all ages with hyperthyroidism treated with radioiodine.[13] The development of atrial fibrillation is one well recognised complication of overt hyperthyroidism, which might be expected to increase circulatory events, especially since atrial fibrillation in association with thyrotoxicosis has embolic complications in about 15% of cases.[14] Furthermore, the frequency of atrial fibrillation complicating thyrotoxicosis increases with age, whereas the likelihood of restoration of sinus rhythm after antithyroid treatment falls with age.[15] In our study a rise in deaths caused by circulatory diseases largely indicated an increase in cardiovascular deaths, although we also saw non-significant increases in mortality due to cerebrovascular diseases. In addition to atrial fibrillation, increased cardiovascular mortality is likely to suggest other adverse effects of subclinical hyperthyroidism on the cardiovascular system. We and others have reported effects of subclinical hyperthyroidism (secondary to thyroxine treatment) on resting pulse, blood pressure, and left ventricular systolic and diastolic function, as well as left ventricular size.[8,16,17]

The excess mortality that we recorded in individuals with subclinical hyperthyroidism did not arise because of overt thyroid hormone excess, since none of the three individuals who subsequently developed overt hyperthyroidism died during follow-up. Similar findings were evident in those with low but detectable thyrotropin and in those with undetectable thyrotropin, suggesting that even mild thyroid hormone excess predicts excess mortality. Reduction in serum thyrotropin, in the absence of thyroxine therapy, and therefore indicating mild endogenous thyroid hormone excess, is a frequent finding in elderly people, and in individuals with goitre or a previous history of hyperthyroidism.[1,6]

Our findings lend support to the view that people with persistently reduced concentrations of thyrotropin in the serum should be considered for treatment (typically with radioactive iodine) to restore biochemically normal thyroid function, with the objective of reducing the described increase in circulatory mortality. A prospective trial needs to be done to assess this intervention. We have not addressed the question of whether subclinical hyperthyroidism secondary to thyroxine replacement therapy is similarly associated with excess mortality or whether careful titration of the dose of thyroxine, with attendant implications for cost and compliance, is important.

Contributors

J V Parle, M C Sheppard, and J A Franklyn planned the project and supervised its execution, analysis, and writing. P Maisonneuve and P Boyle advised on study design and did the statistical analyses. All authors contributed to the writing and preparation of the report.

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