Relationship Between Circulating Thyroid-Stimulating Hormone, Free Thyroxine, and Free Triiodothyronine Concentrations and 9-Year Mortality in Euthyroid Elderly Adults

Article *in* Journal of the American Geriatrics Society · March 2016

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J Am Geriatr Soc. Author manuscript; available in PMC 2017 March 01.

Published in final edited form as:

J Am Geriatr Soc. 2016 March ; 64(3): 553–560. doi:10.1111/jgs.14029.

Relationship Between Circulating Concentrations of Thyrotropin, Free Thyroxine, and Free Triiodothyronine and 9-Year Mortality in Euthyroid Elderly Subjects

Graziano Ceresini, MD, PhD[1], **Michela Marina, MD**[1], **Fulvio Lauretani, MD**[2], **Marcello Maggio, MD, PhD**[1], **Stefania Bandinelli, MD**[3], **Gian Paolo Ceda, MD**[1], and **Luigi Ferrucci, MD, PhD**[4]

[1] Department of Clinical and Experimental Medicine, Endocrinology of Aging Unit, University Hospital of Parma, Italy

[2] Geriatric Unit, University Hospital of Parma, Italy

[3] Geriatric Unit, ASF Toscana, Firenze, Italy

[4] National Institute on Aging, Baltimore, MD, USA.

Abstract

Objectives—Thyroid dysfunction in the elderly is associated with adverse clinical outcomes, with mortality being associated with low TSH. However, it is still unknown whether variability of thyroid function test within the reference range is associated with mortality in older adults. We studied the association between plasma levels of TSH, free T3 (FT3), and free T4 (FT4), and all-cause mortality in older adults who had all three hormones within the normal range.

Design—Longitudinal study

Setting—Community-based

Participants—Total of 815 euthyroid participants of the InCHIANTI study, aged 65 years or older

Measurements—All subjects had TSH, FT3, and FT4 within the reference range at baseline. Plasma TSH, FT3 and FT4 were predictors and 9-year all-cause mortality was the outcome. Cox proportional hazards models adjusted for confounders were used to examine the relationship between quartiles of TSH, FT3, and FT4 and all-cause mortality over 9 years of follow-up.

Results—During the follow-up (mean persons-years 8643.74 [min-max, 35.36-16985.00]), 181 deaths occurred (22.2%). Participants with TSH in the lower quartile had higher mortality than the rest of the population. After adjusting for multiple confounders, participants with TSH in the

Corresponding author and person to whom reprint request should be addressed: Graziano Ceresini, MD, PhD, Department of Clinical and Experimental Medicine, Endocrinology of Aging Unit, Via Gramsci, 14-43126 Parma, Italy, Ph: 011-39-0521-703304, Fax: 011-39-0521-703324, ceresini@unipr.it.

Author Contributions: All Authors contributed in study concept and design, acquisition of subjects and/or data, analysis and interpretation of data, and preparation of manuscript.

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

lowest quartile (Hazard Ratio: 2.22; 95% Confidence Interval: 1.19–4.22) had significantly higher all-cause mortality than those with TSH in the highest quartile. Neither FT3 nor FT4 were associated with mortality.

Conclusions—In euthyroid elderly subjects, normal-low TSH represents an independent risk factor for all-cause mortality.

Keywords

euthyroid; elderly; mortality

INTRODUCTION

Thyroid function abnormalities are frequently observed in aging populations (1-3) with the most prevalent types being represented by subclinical hyper-and hypothyroidism (4,5).

Subclinical hypothyroidism, defined as elevated serum thyrotropin (TSH) concentrations with serum free thyroxine (FT4) concentrations within the reference range, has been associated with negative outcomes such as abnormal serum lipid profile (6) and increased risk of coronary heart disease if TSH exceeds 10 mIU/L (7,8). Subclinical hyperthyroidism, defined as low or suppressed serum TSH concentrations with serum FT3 and FT4 concentrations within the reference range, has been associated with several adverse clinical outcomes, especially in older subjects, mainly represented by abnormalities of cardiovascular system, bone metabolism, blood coagulation and cognition (5,9,10) as well as with increased mortality (10-12). Recent emerging data have suggested that even within the normal reference range, variations of TSH and /or thyroid hormone concentrations may be associated with adverse clinical outcomes. Thyrotropin levels within the reference range but close to the lower limit of the normal values have been shown to be associated with an increased risk of hip fractures in euthyroid women aged 65 years or older (13) and with an increased risk of atrial fibrillation (14). Higher FT_4 levels within the normal reference range have been related to decreased bone mineral density at lumbar spine in peri-menopausal women (15) and with an increased risk of atrial fibrillation (14, 16). Normal/high TSH has been associated with chronic kidney disease (17) and abnormal lipid profile (18). Whether all these adverse clinical characteristics which in euthyroid subjects are associated with variations of thyroid hormone and/or TSH circulating concentrations are life-threatening, is not clearly addressed at present. This issue may be of particular interest in elderly individuals in whom the occurrence of adverse effects of thyroid function variations within the normal reference range might further affect the complexity of the clinical picture often already affected by severe co-morbidity and frailty. In this study we examined the relationship between baseline circulating concentrations of TSH, FT3, and FT4 and both all-cause and cardiovascular mortality during a 9-year follow-up in euthyroid elderly subjects who at baseline had all these three hormones within the reference range.

METHODS

Study population

The study participants consisted of men and women, aged 65 and older, who participated in the Invecchiare in Chianti, “Aging in the Chianti Area” (InCHIANTI) study, conducted in two small towns in Tuscany, Italy. The rationale, design, and data collection have been described elsewhere, (27). Briefly, in August 1998, 1,270 people aged 65 years and older were randomly selected from the population registry of Greve in Chianti (pop. 11,709) and Bagno a Ripoli (pop. 4,704), and of 1,256 eligible subjects, 1,155 (90.1%) agreed to participate. Participants received an extensive description of the study and participated after written, informed consent. The study protocol complied with the Declaration of Helsinki and was approved by the Italian National Institute of Research and Care on Aging Ethical Committee. Of the 1,155 participants, 1,043 (90.3%) participated in the blood drawing. Plasma and serum were frozen in −80°C freezers for hormonal evaluations. Complete data on thyroid hormones were available at baseline in 968 (92.8%) participants. For the analyses presented here, we excluded participants who were on chronic treatment with drugs known to affect thyroid function, including thyroid hormone preparations, methimazole, propylthiouracil, amiodarone, and lithium (total number of subjects excluded = 8), those with elevated FT4 with normal TSH (total number of subjects excluded = 2), those with elevated FT3 with normal TSH (total number of subjects excluded = 1), as well as those who were affected by low-T3 syndrome (total number of subjects excluded = 6). The final study population included, at baseline, 951 subjects aged 65 years and older. Of these, 83 and 29 were excluded because affected by subclinical hyper- and hypothyroidism, respectively, 15 and 5 because of overt hyper- and hypothyroidism, respectively. Four subjects were not included in the present analysis because their follow-up vital status could not be ascertained.

Participants were evaluated again for a three-year follow-up visit from 2001–2003 (n= 926), six-year follow-up visit from 2004–2006 (n= 844), and nine-year follow-up from 2007-2010 (n=634). At the end of the filed data collection, we collected data on mortality of the original InCHIANTI cohort, using data from the Mortality General Registry maintained by the Tuscany Region and the death certificates that were deposited immediately after the death at the Registry office of the Municipality of residence.

Laboratory measures at baseline—Blood samples were collected in the morning after a 12-h fast. Aliquots of serum and plasma were immediately obtained and stored at −80° C. Plasma concentrations of TSH, free triiodothyronine (FT3), and free thyroxine (FT4) were measured using a chemiluminescent immunoassay (Vitros Reagent, Ortho-Clinical Diagnostics, Johnson & Johnson Medical Section, Milan, Italy). Reference normal ranges were 0.46 to 4.68 mIU/L for TSH, 2.77 to 5.27 pg/mL for FT3, and 0.77 to 2.19 ng/dl for FT4. Assay sensitivities were 0.003 mIU/L for TSH, 0.39 pg/mL for FT3, and 0.03 ng/dL for FT4. Intra-assay coefficients of variation (CVs) were 3.9% to 5.3% over the range 0.06 - 80.11 mIU/L for TSH, 4.4% to 5.1% over the range 2.86 - 11.90 pg/mL for FT3, and 4.5% to 5.3% over the range 0.61 - 3.90 ng/dL for FT4. Interassay CVs were less than 9% for all three hormones. Euthyroidism was defined as plasma TSH concentrations between 0.46 and

4.68 mIU/L. Thyroid function tests were measured in 2005. Thyroid function test results were not provided to participants.

Other covariates

Demographic information and information on smoking and medication use were collected using standardized questionnaires. All participants were examined by a trained geriatrician. Diseases were ascertained according to standard, pre-established criteria and algorithms that combine information from self-reported physician diagnoses, current pharmacological treatment, medical records, clinical examinations and blood tests (19).

Weight was measured using a high-precision mechanical scale. Standing height was measured to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Smoking status was assessed according to self-reported data. Smoking history was determined based on self-reports, and participants were categorized into never smokers, former smokers, and current smokers (20). Educational level was recorded as years of school. Cognitive function was evaluated using the Mini-Mental State Examination, and the total score was adjusted for educational level and age (21). The level of physical activity in the 12 months prior to the interview was assessed through an interviewer-administered questionnaire and was coded as sedentary (inactivity or light-intensity activity less than 1 h/week), light physical activity (light-intensity activity 2–4 h/week), and moderate-high physical activity (light-intensity activity ≥ 5 h/week or moderate activity ≥ 1–2 h/week) (22).

Ascertainment of events

Information about deaths was obtained from reviews of medical records, registers of municipality, autopsy reports. Ascertainment of mortality in the InCHIANTI study was 100%. The incident events in this report occurred after baseline and through 2009 with a mean duration of follow-up of nine years with a mean persons-years of follow-up of 8643.74 (min-max, 35.36-16985.00). Cardiovascular mortality, based on underlying cause of death, was defined as any cardiovascular mortality and coded using the International Classification of Diseases, 9th Revision (ICD-9 codes: 390-459).

Statistical analysis

Variables are reported as means (SDs) or as percentages. TSH values were found to be not normally distributed, therefore we introduced the TSH in the regression analysis after its log transformation. To test the nonlinearity relationship between TSH and all-cause mortality, we introduced a quadratic term of Log (TSH) in the regression analysis. Given the departure from linearity of the relationship between TSH and all-cause mortality, the cox proportional hazards models were used to examine the relationship between quartiles of plasma concentrations of TSH and all-cause mortality over 9 years of follow-up. Characteristics of subjects were compared across quartiles of plasma concentrations of TSH using parametric (ANOVA) and non-parametric (Wilcoxon signed-rank test) test as appropriate. Multivariable Cox proportional hazards model, adjusted for age, sex and other variables that were significant in the univariate analyses was used to evaluate the relationship between

hormonal status and mortality. All analyses were performed by the SAS statistical package, version 9.1 (SAS Institute Inc, Cary, North Carolina) with a type I error of 0.05

RESULTS

When levels of log-transformed TSH were considered as continuous variables they were not associated with all-cause mortality (age- and sex-adjusted p=0.07) (data not shown); however, we found a nonlinear relationship between log-transformed TSH and all-cause mortality (age- and sex-adjusted P of the quadratic term of log- transformed TSH=0.035) (data not shown). Therefore, we used TSH quartiles in our analyses.

The characteristics of the participants across quartiles of plasma TSH concentrations are listed in Table 1. There were significantly more men in the lowest quartiles of TSH. Current smoking was higher among participants in the lowest quartile of TSH compared with the higher quartiles. Triglicerydes and physical activity were higher among participants in the highest quartile of TSH compared with the lower quartiles. There were no significant differences across the quartiles of TSH concentrations by age, education, MMSE score, BMI, CRP, total cholesterol, HDL- cholesterol, LDL- cholesterol, or by prevalence of hypertension, heart failure, stroke, cancer, chronic kidney disease, and diabetes, while a reduction in the prevalence of coronary artery disease close to the statistical significance was found in participants in the highest quartile of TSH.

The characteristics of the participants across quartiles of plasma FT4 concentrations are listed in Table 2. There were more female in the highest quartile of FT4. Age of participants, physical activity and HDL-cholesterol were higher among participants in the highest quartile of FT4 compared with the lowest quartile. The prevalence of CHF, atrial fibrillation, hypertension, and chronic kidney disease was higher among participants in the highest quartile of FT4 compared with the lower quartiles. A reduced MMSE score (i.e. <24) was more frequently observed among participants in the highest quartile of FT4. There were no differences across the quartiles of FT4 concentrations by education, total cholesterol, LDL-cholesterol, triglycerides, BMI, CRP, smoke, or by prevalence of coronary artery disease, cancer, stroke, and diabetes.

The characteristics of the participants across quartiles of plasma FT3 concentrations are listed in Table 3. There were significantly more men in the highest quartile of FT3. Age of participants, total cholesterol, LDL-cholesterol, HDL-cholesterol, BMI, and moderate physical activity were higher in the highest quartile of FT3 plasma concentrations compared with the lowest quartile. A reduced MMSE score (i.e. <24) was more frequently observed among participants in the lowest quartile of FT3. The prevalence of cancer and diabetes was higher among participants in the lowest quartile of FT3 compared with the highest quartile. The prevalence of chronic kidney disease was higher among participants in the higher quartile of FT3 compared with the lower quartile. There were no significant differences across the quartiles of FT3 concentrations by education, triglycerides, CRP, smoke, or by prevalence of CHF, coronary artery disease, stroke, atrial fibrillation, and hypertension. During 9 years of follow-up, 181 (22.2%) deaths occurred of which 36 (4.4%) due to cardiovascular causes.

The proportion of participants who died was significantly higher in the lowest quartile of TSH compared with the highest quartile, in the highest quartile of FT4 compared with the lowest quartiles, and in the lowest quartiles of FT3 compared with the higher quartiles. The baseline characteristics of the participants by vital status during follow-up are listed in Table 4. Participants who died were older, with higher CRP, lower physical activity, slightly lower FT3 plasma concentrations and lower HDL-cholesterol levels. A higher proportion of those who died had MMSE score lower than 24, heart failure, stroke, cancer, hypertension, and chronic kidney disease. There were no significant differences between participants who died during the study period and those who did not in education, current smoking, total and LDL-cholesterol, BMI, sex, or by prevalence of diabetes and coronary artery disease.

Levels of TSH in the lowest quartile were significantly associated with mortality in models adjusting for age, sex, BMI, CHF, stroke, cancer, physical activity, hypertension, HDL-cholesterol, triglycerides, CRP, MMSE score, and chronic kidney disease (Hazard Ratio: 2.22; 95% Confidence Interval: 1.19–4.22) (Table 5).

In age- and sex-adjusted model, a significant increase in all-cause mortality was observed for the lowest quartiles of FT4 compared with the highest quartile and for the lowest quartiles of FT3 compared with the highest quartile. However, no significant differences in all-cause mortality was observed among quartiles of FT4 (highest vs lowest quartile HR, 0.59 [95% C.I., 0.30-1.13], P=0.11) and FT3 (highest vs lowest quartile HR, 0.95 [95% C.I., 0.48-1.88], P=0.88) in the fully adjusted model.

DISCUSSION

In this prospective population-based study we evaluated the relationship between TSH, FT4, and FT3 within the normal reference range and mortality in euthyroid elderly subjects. We found that, after a 9-year follow-up, participants who at baseline had plasma TSH concentrations in the lowest quartile of the normal range had a more than 2-fold increased risk of all-cause mortality compared with those whose basal TSH concentrations were in the highest quartiles.

Increased thyroid function has been associated with increased mortality in elderly individuals (5,8,10). However, although adverse clinical consequences of thyroid function variation in euthyroid subjects are acknowledged (23), whether mortality is influenced by TSH and/or free thyroid hormone variations within the normal reference range in euthyroid elderly subjects is still poorly addressed. In this perspective, this study helps to address this issue. The fact that, in our study, euthyroid elderly subjects who at baseline had their TSH in the lowest quartile of the normal range were more likely to die at the 9-year follow-up gives further support to the hypothesis of a negative role played by low TSH in elderly people. The association between low TSH and increased mortality may be clearly accepted for TSH circulating concentrations below the lower reference range, but it appears more difficult to be comprehended when TSH, though low, is within the normal reference range. However, it is important to note that TSH distribution progressively shifts toward higher concentrations with age while free thyroid hormone concentrations remain stable (24-27). This phenomenon may be related to a reduced sensitivity of the pituitary gland to the thyroid

hormone feed-back or to altered TSH bioactivity or reduced sensitivity of the thyroid to TSH, with the result of an increase in TSH circulating concentrations to maintain the homeostasis of thyroid function (26). Up to now, no age-specific range for TSH is commonly used in clinical practice and also the vast majority of studies performed in elderly subjects, including the present one, did not consider any age-related ranges for defining TSH normal values in older adults. In this perspective, although with the limitation of the observational nature of this study, our results would support further research addressing whether reference range for TSH should be shifted to higher values in older subjects.

Among participants in the highest quartile of FT4 we found a higher prevalence of negative cardiovascular outcomes. These data are in line with recent reports by Cappola et al. (28) who demonstrated higher incidences of atrial fibrillation, coronary heart disease, and heart failure in elderly euthyroid subjects with high/normal FT4. On the contrary, we did not find any differences in cardiovascular parameters among quartiles of FT3. Since in the majority of the available reports on thyroid status and adverse outcomes FT3 is rarely reported, it is difficult to compare the results of our study to the literature. However, our data are in agreement with recent reports on the lack of association between T3 and cardiovascular outcomes in elderly euthyroid subjects (28). We should note, however, that given the small number of cardiovascular deaths in our cohort, we could not draw any definitive conclusion on the association between thyroid function test parameters and cardiovascular mortality.

When we compared baseline characteristics of study participants by vital status during 9 years of follow-up (i.e., survived vs died) we found no differences in circulating TSH. This might be due to the nonlinear relationship between TSH and mortality in our population. Participants who died had more frequently a borderline significant higher FT4. This is in line with the reports of the literature which suggest a protective effects of low FT4 on clinical outcomes in the elderly (29) and with recent experiences which demonstrate an association between FT4 and mortality in euthyroid elderly subjects (28).

Circulating FT3 was lower in subjects who died. We don't have an explanation for this finding. A possibility is that low FT3 may be related to the presence of conditions similar to those that determine the low-T3 syndrome which may be associated with increased mortality.

In age- and sex-adjusted evaluations, higher FT4 quartile and lower FT3 quartiles were associated with 9-year all-cause mortality. These associations, however, were not confirmed in the fully-adjusted model. These results, would not be in contrast with the hypothesis of a mild thyroid hyperfunction reflected by the normal-low TSH in our euthyroid subjects, a condition which is best indicated by TSH, rather than free thyroid hormone concentrations.

It has been recently reported that in euthyroid elderly men all-cause mortality is associated with higher FT4 but not TSH variations (30). Our study differs from the study reported above in several points. First, in that study only men were examined, so it is difficult to draw any conclusions for the general population. Furthermore, in the study mentioned above FT3 was not measured, therefore a low-T3 syndrome could not be excluded and this could have significantly affected results. Also, the present study is characterized by a longer duration of

the follow-up (i.e., 9.17±0.21 years [mean±SD] in the present study vs. 6.4±1.5 years in the study reported above) and a wider age range (i.e., 65-98 years in the present study vs.70-89 years in the study reported above).

Given that the current work cannot demonstrate causal relationship between low-normal TSH and mortality, whether our participants with TSH values in the lowest quartile of the normal range indeed represent a population of subjects with a somewhat increased thyroid function is not addressed by the present study. In this perspective, other causes of low TSH (i.e., pituitary disorders or a low TSH state associated with an overt inflammatory condition) should be taken into account. However, it is of interest to note that our subjects reside in a geographic area with moderate iodine deficiency (31); in this context, low TSH, even within the normal reference range, might indeed represent the spectrum of a mild thyroid hyperfunction, possibly due to autonomous thyroid nodules. To this regard, the fact that in our study TSH thresholds might be affected, at least theoretically, by the moderate iodine intake of our population represents a critical point to be considered before a generalization of our results is granted.

The strength of this study is that all subjects of the cohort with overt or subclinical thyroid dysfunctions as well as those taking medications known to affect thyroid function were accurately excluded from analyses and that, in addition to TSH, all participants of our cohort had both FT3 and FT4 measured. This allowed an accurate exclusion from analyses of subjects with low-T3 syndrome, thus avoiding any interference of this condition on results. Other points of strength of the present study are represented by the duration of the follow-up (i.e., 9 years) and the fact that ascertainment of mortality in the InCHIANTI cohort was 100%.

One major limitation of this study is represented by the fact that only baseline thyroid function tests are available, so we do not know whether thyroid function tests were stable, or rather were characterized by any modifications during the follow-up. However, this is a characteristic shared by many epidemiological studies on these topics.

In conclusion, our results suggest that low TSH within the reference range may be associated with mortality in older adults. These data further support the debate on the possibility that the shift of the reference range for higher TSH can be clinically advantageous for elderly people including those treated with l-thyroxine for hypothyroidism. Further studies are needed to better address this issue and to identify the TSH thresholds optimal for elderly subjects, including the oldest old.

ACKNOWLEDGMENT

Funding Sources: This work was supported as a “target project” (ICS 110.1|RS97.71) by the Italian Ministry of Health and, in part, by the U.S. National Institute on Aging (contracts 263_MD_9164_13 and 263_MD_821336), and by grant n. FIL0774249 from MURST, Rome (Graziano Ceresini, MD, PhD)

Sponsor's Role: None

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J Am Geriatr Soc. Author manuscript; available in PMC 2017 March 01.

Table 1

Baseline characteristics of study participants by quartiles of TSH (n=815)

		Quartiles of TSH mIU/L				P*
		<0.93	0.93 - 1.35	1.35 - 1.93	>1.93	
		(n = 203)	(n = 203)	(n = 203)	(n = 204)	
Age (years) (mean ± SD)		74.5 ± 6.6	74.7 ± 6.8	75.9 ± 7.7	76.6 ± 7.8	0.08
Men n (%)		97 (48.3)	96 (46.8)	92 (45.1)	74 (36.1)	0.01
Education (years) (mean ± SD)		5.3 ± 3.3	5.32 ± 3.61	5.6 ± 3.6	5.8 ± 3.6	0.44
Total Cholesterol (mg/dl) (mean ± SD)		216.0 ± 37.7	219.2 ± 39.0	217.4 ± 42.9	221.0 ± 38.9	0.73
LDL Cholesterol (mg/dl) (mean ± SD)		136.3 ± 32.6	137.1 ± 33.8	136.3 ± 36.6	138.0 ± 34.6	0.97
HDL Cholesterol (mg(dl) (mean ± SD)		55.5 ± 14.3	56.6 ± 16.0	56.5 ± 16.4	54.7 ± 15.2	0.22
Triglycerides (mg/dl) (mean ± SD)		121.0 ± 60.3	126.9 ± 65.4	122.7 ± 63.8	141.5 ± 86.7	0.01
BMI (Kg/m2) (mean ± SD)		26.8 ± 3.6	27.5 ± 4.2	27.5 ± 4.1	27.4 ± 4.1	0.30
CRP (mg/L) (mean ± SD)		4.3 ± 5.2	5.2 ± 11.6	5.8 ± 10.6	4.9 ± 6.8	0.44
CHF n, (%)		44 (21.9)	38 (18.5)	34 (16.7)	39 (19.0)	0.59
Coronary artery disease n, (%)		15.0 (7.5)	19.0 (9.3)	14.0 (6.9)	7.0 (3.4)	0.07
Cancer n, (%)		11 (5.5)	12 (5.8)	11 (5.4)	19 (9.3)	0.16
Stroke n, (%)		15 (7.5)	13 (5.5)	19 (9.4)	15 (7.3)	0.78
Atrial Fibrillation n, (%)		4 (2.0)	10 (4.9)	4 (1.9)	6 (2.9)	0.98
Hypertension n, (%)		105 (52.2)	94 (45.8)	87 (42.7)	106 (51.7)	0.98
Chronic kidney disease n, (%)		83.0 (41.3)	79.0 (38.5)	82.0 (40.2)	99.0 (48.5)	0.14
Participants with MMSE<24 n, (%)		48 (23.9)	58 (28.3)	59 (28.9)	56 (27.3)	0.44
Diabetes n, (%)		29 (14.4)	18 (8.9)	21 (10.3)	22 (10.7)	0.98
Current Smoking (%)						0.01
	Never Smoked	53.7	55.6	58.8	65.8	
	Former Smoker	27.9	30.2	27.5	21.5	
	Actual Smoker	30.8	14.2	13.7	12.7	
Level of Physical Activity (%)						0.03
	Light	5.5	7.3	3.4	4.4	
	Moderate	77.1	73.2	75.9	70.2	

		Quartiles of TSH mIU/L				P*
		<0.93 (n = 203)	0.93 - 1.35 (n = 203)	1.35 - 1.93 (n = 203)	>1.93 (n = 204)	
	High	17.4	19.5	20.6	25.4	
Deceased (All-cause mortality) (%)		28.7	20.3	23.4	24.0	0.02

BMI, Body Mass Index

CRP, C-reactive Protein; CHF, Chronic Heart Failure

* Age- and sex-adjusted (where appropriate)

J Am Geriatr Soc. Author manuscript; available in PMC 2017 March 01.

Table 2

Baseline characteristics of study participants by quartiles of FT4 (n=815)

		Quartiles of FT4 ng/mL				P*
		<1.25	1.25 - 1.42	1.42 - 1.60	> 1.60	
		(n = 203)	(n = 203)	(n = 203)	(n = 204)	
Age (years) (mean ± SD)		73.6 ± 6.9	74.5 ± 6.9	75.4 ± 7.4	77.4 ± 7.4	<.0001
Men n (%)		105 (54.7)	99 (48.3)	82 (40.8)	73 (33.6)	<.0001
Education (years) (mean ± SD)		5.7 ± 3.4	5.7 ± 3.5	5.4 ± 3.3	4.9 ± 3.4	0.86
Total Cholesterol (mg/dl) (mean ± SD)		216.6 ± 41.3	217.5 ± 36.2	219.3 ± 40.0	220.0 ± 40.9	0.81
LDL Cholesterol (mg/dl) (mean ± SD)		137.9 ± 34.7	135.6 ± 31.8	136.7 ± 35.1	137.7 ± 35.9	0.80
HDL Cholesterol (mg(dl) (mean ± SD)		52.1 ± 13.9	55.9 ± 16.0	57.5 ± 13.9	57.5 ± 17.4	0.01
Triglycerides (mg/dl) (mean ± SD)		133.0 ± 70.3	130.0 ± 87.1	125.6 ± 58.0	124.1 ± 62.2	0.66
BMI (Kg/m2) (mean ± SD)		27.5 ± 3.8	27.0 ± 3.7	27.4 ± 3.6	27.3 ± 4.7	0.69
CRP (mg/L) (mean ± SD)		5.2 ± 7.4	4.4 ± 10.8	4.5 ± 7.1	6.2 ± 9.6	0.29
CHF n, (%)		6 (3.1)	7 (3.4)	7 (3.5)	18 (8.3)	0.002
Coronary artery disease n, (%)		10 (5.2)	9 (4.4)	17 (8.5)	19 (8.8)	0.06
Cancer n, (%)		14 (7.3)	10 (4.9)	17 (8.5)	12 (5.5)	0.82
Stroke n, (%)		9 (4.7)	7 (3.4)	8 (4.0)	16 (7.4)	0.43
Atrial Fibrillation n, (%)		3 (1.6)	4 (1.9)	5 (2.5)	12 (5.5)	0.02
Hypertension n, (%)		84 (43.8)	98 (47.8)	92 (45.8)	118 (54.4)	0.02
Chronic kidney disease n, (%)		67 (35.0)	88 (42.9)	96 (47.8)	127 (58.7)	0.03
Participants with MMSE<24 n, (%)		47 (21.3)	52 (23.5)	49 (22.2)	73 (33.0)	0.05
Diabetes n, (%)		23 (12.0)	20 (9.8)	12 (6.0)	35 (16.1)	0.82
Current Smoking (%)						0.07
	Never Smoked	105	115	115	142	
	Former Smoker	62	52	55	49	
	Actual Smoker	25	38	31	26	
Level of Physical Activity (%)						<.0001
	Light	33	32	38	66	
	Moderate	146	158	155	145	

		Quartiles of FT4 ng/mL				P*
		<1.25	1.25 - 1.42	1.42 - 1.60	> 1.60	
		(n = 203)	(n = 203)	(n = 203)	(n = 204)	
	High	13	15	8	6	
Deceased (All-cause mortality) (%)		18.3	18.8	22.7	32.7	0.0002

BMI, Body Mass Index

CRP, C-reactive Protein; CHF, Chronic Heart Failure

*Age- and sex-adjusted (where appropriate)

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Table 3

Baseline characteristics of study participants by quartiles of FT3

		Quartiles of FT3 pg/mL				P*
		<3.97	3.97 - 4.21	4.21 - 4.52	> 4.52	
		(n = 203)	(n = 203)	(n = 203)	(n = 204)	
Age (years) (mean ± SD)		77.4 ± 8.6	75.4 ± 7.0	74.3 ± 6.5	74.2 ± 6.7	<.0001
Men n (%)		71 (36.6)	86 (41.1)	93 (45.8)	109 (52.2)	0.01
Education (years) (mean ± SD)		5.4 ± 3.5	5.2 ± 2.9	5.6 ± 3.5	5.7 ± 3.7	0.45
Total Cholesterol (mg/dl) (mean ± SD)		211.1 ± 38.1	214.5 ± 39.1	222.1 ± 36.7	225.4 ± 4.3	0.0002
LDL Cholesterol (mg/dl) (mean ± SD)		131.2 ± 32.7	134.2 ± 33.4	140.8 ± 33.6	141.2 ± 36.8	0.009
HDL Cholesterol (mg(dl) (mean ± SD)		54.2 ± 15.1	56.0 ± 14.9	55.6 ± 15.9	57.4 ± 15.9	0.03
Triglycerides (mg/dl) (mean ± SD)		128.2 ± 86.0	121.5 ± 62.2	128.3 ± 58.3	134.3 ± 72.1	0.35
BMI (Kg/m2) (mean ± SD)		26.8 ± 4.0	27.1 ± 3.9	27.3 ± 4.2	27.9 ± 3.8	0.04
CRP (mg/L) (mean ± SD)		5.9 ± 12.5	5.7 ± 10.5	4.2 ± 5.4	4.6 ± 5.4	0.29
CHF n, (%)		8 (4.1)	10 (4.8)	10 (4.9)	10 (4.8)	0.94
Coronary artery disease n, (%)		19 (9.8)	9 (4.3)	16 (7.9)	11 (5.3)	0.21
Cancer n, (%)		21 (10.8)	9 (4.3)	13 (6.4)	10 (4.8)	0.04
Stroke n, (%)		11 (5.7)	8 (3.8)	10 (4.9)	11(5.3)	0.55
Atrial Fibrillation n, (%)		5 (2.6)	5 (2.4)	5 (2.5)	9 (4.3)	0.31
Hypertension n, (%)		82 (42.3)	95 (45.5)	105 (51.7)	110 (52.6)	0.78
Chronic kidney disease n, (%)		76 (39.2)	74 (35.4)	83 (39.4)	85 (40.7)	0.0002
Participants with MMSE<24 n, (%)		63 (32.5)	59 (28.2)	49 (24.1)	50 (23.9)	0.04
Diabetes n, (%)		28 (14.4)	23 (11.0)	17 (8.4)	22 (10.5)	0.009
Current Smoking (%)						0.15
	Never Smoked	126	125	114	112	
	Former Smoker	39	50	63	163	
	Actual Smoker	29	34	26	31	
Level of Physical Activity (%)						0.01
	Light	57	43	34	35	
	Moderate	125	155	161	163	

		Quartiles of FT3 pg/mL				P*
		<3.97	3.97 - 4.21	4.21 - 4.52	> 4.52	
		(n = 203)	(n = 203)	(n = 203)	(n = 204)	
	High	12	11	8	11	
Deceased (All-cause mortality) (%)		31.4	26.8	14.3	16.7	<.0001

BMI, Body Mass Index

CRP, C-reactive Protein

CHF, Chronic Heart Failure

*Age- and sex-adjusted (where appropriate)

Table 4

Baseline characteristics of study participants by vital status during 9 years of follow-up

		Survived	Died	P*
		n=634	n=181	
Age (years) (mean ± SD)		73.26 ± 5.90	82.43 ± 7.20	<.0001
Men n, (%)		269 (42.4)	90 (49.7)	0.08
Education (years) (mean ± SD)		5.72 ± 3.36	5.61 ± 3.40	0.21
TSH (mIU/L) (mean ± SD)		1.53 ± 0.83	1.56 ± 0.91	0.64
FT3 (pg/mL) (mean ± SD)		4.27 ± 0.41	4.07 ± 0.47	0.008
FT4 (ng/dL) (mean ± SD)		1.42 ± 0.26	1.54 ± 0.38	0.09
BMI (Kg/m2) (mean ± SD)		27.42 ± 4.01	26.77 ± 3.92	0.85
CRP (mg/L) (mean ± SD)		4.33 ± 6.12	7.81 ± 14.9	0.008
CHF (n, %)		103 (16.2)	52 (28.7)	<.0001
Coronary artery disease n,(%)		41 (6.5)	14 (7.7)	0.54
Atrial Fibrillation n,(%)		11 (17)	13 (7.2)	0.001
Hypertension n,(%)		295 (46.5)	97 (53.6)	0.002
Chronic kidney disease n,(%)		233 (60)	90 (55)	<.0001
Participants with MMSE<24 n,(%)		130 (21)	91 (50.3)	<.0001
Diabetes n,(%)		75 (12)	29 (16)	0.15
Total Cholesterol (mg/dl) (mean ± SD)		221.64 ± 38.6	207.00 ± 41.14	0.08
LDL Cholesterol (mg/dl) (mean ± SD)		139.47 ± 33.90	128.08 ± 34.61	0.21
HDL Cholestorol (mg/dl) (mean ± SD)		56.65 ± 15.09	53.00 ± 16.58	0.01
Triglycerides (mg/dl) (mean ± SD)		127.63 ± 68.8	129.60 ± 75.1	0.34
Cancer n, (%)		40 (6.3)	13 (7.2)	<.0001
Stroke n, (%)		18 (2.8)	22 (12.2)	<.0001
Current Smoking n, (%)		94 (15)	26 (14)	0.84
Level of Physical Activity n, (%)				
	Light	86 (13.6)	83 (45.9)	<.0001
	Moderate	510 (80.4)	94 (51.9)	
	High	38 (6.0)	4 (2.2)	

J Am Geriatr Soc. Author manuscript; available in PMC 2017 March 01.

BMI, Body Mass Index

CRP, C-reactive Protein

CHF, Chronic Heart Failure

* Age- and sex-adjusted (where appropriate)

Table 5

Relationship between quartiles of TSH and all-cause mortality in separate multivariable Cox proportional hazard models

Model 1	**HR**	**95% C.I.**	**P**
TSH			
< 0.93	1.90	1.09-3.33	0.02
0.93 - 1.35	0.67	0.37-1.24	0.20
1.35 - 1.93	1.21	0.69-2.14	0.50
> 1.93	--	--	--
Age	1.23	0.69-2.13	<.0001
Sex (men vs women)	0.42	0.28-0.64	<.0001
Model 2			
TSH			
< 0.93	2.22	1.19-4.22	0.01
0.93 - 1.35	0.71	0.35-1.45	0.34
1.35 - 1.93	1.35	0.70-2.58	0.37
> 1.93	--	--	--
Age	1.22	1.17-1.27	<.0001
Sex	0.48	0.27-0.87	0.01
BMI	1.01	0.94-1.07	0.98
Stroke	1.96	1.29-2.97	0.002
Cancer	1.04	0.42-2.57	0.94
Levels of Physical Activity	0.52	0.31-0.87	0.01
Hypertension	1.18	0.75-1.87	0.47
HDL Cholesterol	0.99	0.98-1.00	0.31
CRP	1.02	0.99-1.05	0.18
Chronic Kidney Disease	1.15	0.97-1.37	0.12
Triglycerides	1.00	0.99-1.01	0.74

Model 1: age and sex adjusted model

Model 2: fully adjusted model

BMI, Body Mass Index

CRP, C-reactive Protein