# Chapter 4

# Thyroid status and mortality

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Ogliari G, Smit RA, van der Spoel E, Mari D, Torresani E, Felicetta I, Lucchi TA, Rossi PD, van Heemst D, de Craen AJ, Westendorp RG. Thyroid status and mortality risk in euthyroid older adults: sex-differences in the Milan Geriatrics 75+ Cohort Study.

**ABSTRACT**

**Background**: Optimal thyroid status in old age is controversial. This study investigated the longitudinal association between thyroid parameters and 10-year all-cause mortality risk in euthyroid older outpatients according to sex and age.

**Methods**: Baseline thyrotropin (TSH), free thyroxine (fT4) and free triiodothyronine (fT3) were assessed in the Milan Geriatrics 75+ Cohort Study. 338 men and 630 women aged over 75 years were euthyroid. Hazard ratios (HRs) and 95% confidence intervals (CI) were calculated for the associations of TSH, fT4 and fT3 with mortality risk using Cox regression. Analyses were stratified by sex and adjusted for socio-demographic factors and co-morbidities.

**Results**: 245 men and 382 women died during follow-up. After adjustment, each 1 mU/L higher TSH was associated with decreased mortality risk in men (HR 0.81, 95% CI 0.68-0.96), but not in women (HR 1.09, 95% CI 0.96-1.23) (p for sex-difference = 0.002). Each 1 ng/L higher fT4 was associated with increased mortality risk in men (HR 1.12, 95% CI 1.03-1.21), whereas not in women (HR 0.99, 95% CI 0.94-1.04) (p for sex-difference = 0.008). Each 1 pg/mL higher fT3 was associated with decreased mortality risk in both men (HR 0.78, 95% CI 0.55-1.10) and women (HR 0.78, 95% CI 0.62-0.99). The inverse association between TSH and mortality was most pronounced in men aged over 85 years.

**Conclusions**: Among euthyroid older outpatients, higher TSH and lower fT4 were associated with decreased mortality risk in men but not in women. When assessing thyroid status, sex and age should be taken into account.

## INTRODUCTION

Thyroid status can be assessed by measuring serum thyrotropin (TSH), free thyroxine (fT4) and free triiodothyronine (fT3). Optimal thyroid status in old age, particularly the normal TSH reference range, is controversial[1,2]. Lowering TSH upper reference limit from 4.00 to 2.50 mU/L is highly debated[3], as TSH distribution progressively shifts towards higher values with aging[4]. This shift may arise from a higher prevalence of occult thyroid disease; indeed, euthyroid adults with higher TSH have an increased risk of hypothyroidism[5]. Alternatively, this shift may result from selective survival of individuals with constitutively lower thyroid status. Indeed, exceptionally long-lived adults and their offspring exhibit higher normal TSH with unchanged fT4, possibly indicative of a different set-point of the pituitary-thyroid axis[6]. A genetic influence on thyroid status is also supported by twin studies[7] and by the observation that intra-individual variation in thyroid status is smaller than inter-individual variation[8]. In addition, sex may modulate the effect of several genetic variants for TSH and fT4 levels[9].

TSH, fT4 and fT3 have profound and pleiotropic effects on aging individuals, by influencing metabolism, cardiovascular function and mental health[10]. These effects may differ in men and women[10,11]. Furthermore, the relationship between TSH and mortality risk in euthyroid adults is unclear, with some studies reporting no association[12,13] and others an inverse association[14-18]. The relationship of fT4 and fT3 with mortality risk is ambiguous[12,15,19]. Finally, most current evidence is from population-based studies on adults with wide age ranges, which limits their generalizability. Data are lacking on older outpatients, a potentially diverse population, whom clinicians encounter in everyday clinical practise. Older outpatients may present a higher burden of comorbidities, in a complex interplay with thyroid status.

Therefore, we assessed the association between thyroid status and mortality risk in euthyroid older men and women enrolled in the Milan Geriatrics 75+ Cohort Study, a longitudinal geriatric outpatient cohort. Furthermore, we investigated whether it differs by sex and age.

## METHOD

### *Study Design and Participants*

The Milan Geriatrics 75+ Cohort Study is a prospective hospital-based cohort study of the outpatients of the Geriatric Unit of ''I.R.C.C.S. Ca' Granda'' in Milan, Italy. Between 3 January 2000 and 25 March 2004, 1861 new consecutive outpatients aged 75 years and over attended a first face-to-face, standardized, structured, comprehensive visit with trained physicians, after informed consent. Details of study design were previously described[20].

To explore the association between the natural course of euthyroid function, unmodified by medical intervention, and mortality, we excluded participants on thyroid medications (n=74), and those with baseline TSH < 0.20 mU/L or > 4.00 mU/L or missing (n=768). Additionally, we excluded participants with missing data on mortality at follow-up (n=51). Therefore, we included 968 euthyroid participants in the present analysis. These included participants were younger and more likely to be men, smokers and to have depression/anxiety compared to the excluded participants (data not shown). Of the included participants, 761 and 708 participants, respectively, had available data on fT4 and fT3; we performed our analyses on fT4 and fT3 in those with values within the reference range (n=736 and n=651, respectively). The study was approved by I.R.C.C.S. Ca' Granda Ethics Committee.

### *Thyroid parameters*

Blood for baseline measurements was drawn in the morning, after an overnight fast. TSH, fT4 and fT3 were measured in serum using chemiluminescent assays (Immulite 2000, Medical Systems). IRCCS Ca' Granda Laboratory reference ranges were 0.20-4.00 mU/L for TSH, 8.0-18.0 ng/L for fT4 and 2.0-4.8 pg/mL for fT3.

### *Co-morbidities and life-style factors*

Baseline data on history of hypertension, diabetes mellitus, coronary heart disease (CHD), transient ischemic attack (TIA) or stroke, atrial fibrillation, claudication and heart failure were obtained from medical documents. Cancer was defined as a diagnosis within the previous five years. Symptoms of anxiety/depression were self-reported or stated in medical documents.

Smoking was dichotomized as never or ever (current and previous). Education was defined as years of school attended. Number of medications was the number of drugs taken chronically or cyclically.

***Mortality***

All-cause mortality was assessed through the Register Office of Milan or other town of residence. The follow-up period was the time between baseline and either death, loss to follow-up or 10-year period.

***Statistical analyses***

Baseline characteristics were reported as mean (standard deviation, SD) for continuous variables and number (percentage) for categorical variables. Differences in baseline characteristics between sexes or across TSH quartiles were assessed using Student's t-test, one-way ANOVA or chi-square test where appropriate. We checked whether fT4 was inversely associated with the logarithm of TSH in our cohort, as previously shown in the literature[21], using linear regression.

We performed Cox regression to estimate hazard ratios (HRs) and 95% confidence intervals (CI) for the association of TSH, fT4 and fT3, respectively, with mortality risk in men and women, separately. First, we tested the presence of linear associations between thyroid parameters and mortality risk. Second, we checked the presence of non-linear associations, by entering thyroid parameters and squared thyroid parameters in the Cox regression as continuous variables. Third, we performed additional analyses using quartiles of TSH, fT4 and fT3. Finally, we ran further analyses using three categories of TSH values, which were defined according to clinical cut-offs (TSH 0.20-0.39; TSH 0.40-2.50; TSH 2.51-4.00 mU/L)[2,22].

To explore sex-differences in the relationship between thyroid parameters and mortality risk, we computed interaction terms by multiplying thyroid parameters, as continuous variables, by sex.

Furthermore, we examined the association between thyroid parameters and mortality risk within three age strata (75–79, 80–84, ≥85 years). We tested for interaction between thyroid

parameters and age, in men and women, separately. Moreover, we checked for sex-differences within age strata.

We performed sensitivity analyses after exclusion of participants who were on medications potentially affecting thyroid function (amiodar or lithium) or who had a history of thyroid disease. Furthermore, we performed sensitivity analyses for the association of TSH with mortality risk restricted to those participants with both fT4 and fT3 within the reference range.

All analyses were performed in two steps. In Model 1, analyses were adjusted for age. In Model 2, they were additionally adjusted for education, smoking, hypertension, diabetes mellitus, atrial fibrillation, CHD, claudication, stroke/TIA, depression/anxiety, cancer and number of medications. Analyses were performed using SPSS version 20.0.0 (SPSS Inc., Chicago, IL).

**RESULTS**

Table 1 shows the baseline characteristics of the participants by sex and across quartiles of TSH. In the cohort, mean age was 82 years (range 75-98) and 630 (65.1%) participants were women. Mean TSH, fT4 and fT3 were 1.7 mU/L, 12.2 ng/L and 2.9 pg/mL, respectively, and did not differ by sex (all p-values > 0.05). Men were more educated, more likely to be smokers, to have atrial fibrillation, CHD, claudication, stroke/TIA or cancer, while less likely to have depression/anxiety compared to women (all p-values < 0.05). Baseline characteristics of men did not differ across quartiles of TSH. In contrast, women with higher TSH were more likely to have a history of stroke/TIA (p-value = 0.004).

We observed an inverse relationship between fT4 and the logarithm of TSH in both men (β= -0.144, 95% CI -0.291;-0.002, p=0.054) and women (β= -148, 95% CI -0.248;-0.047, p=0.004).

After 10-year follow-up, 245 (72.5%) men and 382 (60.6%) women had died. At 10-year follow-up, higher TSH and lower fT4 were linearly associated with decreased mortality risk in men, whereas higher fT3 was linearly associated with decreased mortality risk in women (all p-values < 0.05, Figure 1). At 10-year follow-up, no U-shaped associations were observed (all p-values for quadratic associations >0.05).

In contrast, the association between TSH and 5-year mortality risk in women was U-shaped, even after full adjustment (p-value for quadratic association = 0.009, Supplementary Figure 1).

All other associations at 1-year and 5-year follow-up were similar to those observed at 10-year follow-up (Supplementary Table 1).

Figure 2 shows the effect of sex on the associations of TSH, fT4 and fT3 with 10-year mortality risk. Sex significantly modified the associations of TSH and fT4 with mortality. After full adjustment, each 1 mU/L higher TSH was associated with a 0.81-fold (95% CI 0.68-0.96, p = 0.013) decreased mortality risk in men, whereas not in women (HR 1.09, 95% CI 0.96-1.23, p = 0.206) (p for sex-difference = 0.002). Likewise, each 1 ng/L higher fT4 was associated with a 1.12-fold (95% CI 1.03-1.21, p = 0.008) increased mortality risk in men, whereas not in women (HR 0.99, 95% CI 0.94-1.04, p = 0.660) (p for sex-difference = 0.008). No sex-difference was observed in the relationship between fT3 and mortality. Each 1 pg/mL higher fT3 was associated with decreased mortality risk in men (HR 0.78, 95% CI 0.55-1.10, p =0.151) and women (HR 0.78, 95% CI 0.62-0.99, p = 0.037).

Figure 3 illustrates the influence of age on the association between TSH and mortality risk at 10-year follow-up. After full adjustment, each 1 mU/L increase in TSH was associated with a 0.77-fold (95% CI 0.55-1.08, p = 0.125) and with a 0.63-fold (95% CI 0.46-0.87, p = 0.006) decreased mortality risk in men aged 80-84 years and 85 years and over, respectively. In contrast, the association tended to revert in men aged 75-79 years (HR 1.12, 95% CI 0.82-1.52, p = 0.495). In men, interaction by age was significant (p = 0.006). In women, we observed neither association between TSH and mortality risk in any age strata nor interaction by age.

Sex-differences in the relationship between TSH and mortality risk were not present in participants aged 75-79 years (p = 0.769), whereas they appeared in those aged 80-84 (p = 0.042) and 85 years and over (p = 0.004) (Figure 3).

We found no interaction by age in the relationships of fT4 and fT3 with mortality risk in either men or women (all p > 0.05, data not shown).

Figure 4 shows the association between clinical categories of TSH and 10-year mortality risk by sex. After full adjustment, men with TSH 2.51-4.00 mU/L had a 0.61-fold (95% CI 0.41-0.92, p = 0.017) decreased mortality risk than men in the middle category. In contrast, women with TSH 2.51-4.00 mU/L had a 1.19-fold (95% CI 0.90-1.56, p = 0.221) increased mortality risk than women in the middle category.

The results did not materially change in sensitivity analyses after exclusion of participants taking amiodar (n=22), lithium (n=1) or with previous thyroid disease (n=12) (data not shown). Likewise, the association between TSH and mortality risk remained essentially unchanged when restricting the analyses to participants with both fT4 and fT3 within the reference range (n=632) (data not shown).

## DISCUSSION

Among euthyroid older adults in an outpatient setting, higher TSH and lower fT4 were associated with decreased mortality risk in men, but not in women. The associations of TSH and fT4 with mortality risk significantly differed by sex. The inverse association between TSH and mortality risk was most pronounced in men aged 85 years and over. All associations were independent of cardiovascular risk factors and comorbidities.

Our finding of an inverse relationship between TSH and mortality risk in men is in line with previous population-based studies in older adults[14-18], whereas others showed no association[12,13]. The discrepancies among studies may result from differences in the age- and sex- structure of the studied populations. Indeed, the novelty of our study is to report sex-differences in the relationship between TSH and mortality risk.

Why does sex modify the relationship between thyroid status and mortality? First, women compared to men have higher prevalence and incidence of subclinical and overt thyroid dysfunctions, which have been associated with an excess of mortality[23-25]. TSH values at the upper and lower limits of our laboratory reference range may reflect occult thyroid diseases in women, while not in men. Our finding of a U-shaped relationship between TSH and mortality risk at 5-year follow-up only in women is consistent with this hypothesis. Second, sex modifies the relationship between morbidity and mortality[26]. Women live longer than men, by surviving diseases that are fatal in men[26].

High normal thyroid status, as characterised by lower TSH and higher fT4 within the reference range, has been linked to adverse health outcomes[10]. These may result from different pathophysiological mechanisms, including increased metabolic rate and altered cardiovascular hemodynamic[27]. High normal thyroid status has been linked to increased heart rate and incident atrial fibrillation, which in turn are associated with functional decline and mortality[22,28-29].

Higher fT4 has also been directly related to frailty in euthyroid community-dwelling older men[19,30].

Furthermore, high normal thyroid status may affect brain structure and function. High thyroid status may favour thromboembolism and brain vascular damage through a combination of atrial fibrillation, endothelial dysfunction and hypercoagulability[23]. Alternatively, it may directly cause neurodegeneration through increased oxidative stress[23]. However, controversy persists on the association between thyroid status and cognitive impairment and dementia, which, in turn, have been associated with increased mortality risk[31-34].

High normal thyroid status may be particularly detrimental in older adults with cardiovascular comorbidities[27]. Consistent with this hypothesis, in our cohort, lower TSH and higher fT4 were associated with increased mortality risk in men, especially the oldest men, who presented more cardiovascular comorbidities compared to women. However, sex-differences in our study remained significant after adjustment for comorbidities.

An alternative explanation to our findings may be that the set-point of the pituitary-thyroid axis is shifted towards higher TSH values in adults with genetic predisposition to longevity[6]. Men aged over 85 years in our study had above-average life-expectancy, thus suggesting a genetic longevity trait[35]. Animal studies have suggested a causal relationship between lower thyroid status and extended life span[36]. Lower thyroid status may extend life span by lowering metabolic rate and core body temperature, which in turn results in lower generation of reactive oxygen species and oxidative stress[36]. Other mechanisms may include effects on membrane composition, inflammation and stem cell renewal[37].

Our finding of an association between lower fT3 and increased mortality risk is in line with The Aging in the Chianti Area Study, which included Italians aged 65 years and over[15]. Lower fT3 in euthyroid older individuals may be indicative of non-thyroidal systemic illnesses[15,38].

Our study has relevant clinical implications. First, clinicians should take into account both sex and age when assessing thyroid status. Furthermore, we reported that older men with TSH 2.51 – 4.00 mU/L had a 0.61-fold decreased mortality risk than those with TSH 0.40 – 2.50 mU/L. This observational finding conflicts with the indication of lowering TSH upper reference limit, at least in older men[2].

Moreover, clinical trials on the clinical benefits or harms of lowering TSH upper reference limit in older adults are lacking[39]. Furthermore, clinical trials recruit selected populations, which limits their generalizability[39].

A major strength of our study is our unselected population of older geriatric outpatients, which makes our findings generalizable in common clinical practice. A further asset is the longitudinal design, with a long follow-up. However, the observational nature of our study limits us in inferring causality. Furthermore, a single measurement of thyroid status was used in the analyses, potentially leading to misclassification of subjects. However, previous research has demonstrated that intra-individual variability of thyroid status is narrow and less than inter-individual variability[8]. In addition, this misclassification would be random and merely lead to underestimation of true associations.

In conclusion, higher TSH and lower fT4 within the reference ranges were associated with decreased mortality risk in men but not in women. Our findings add to the current debate on TSH reference limits. Further research is needed to establish whether the relationship between thyroid status and mortality is causal.

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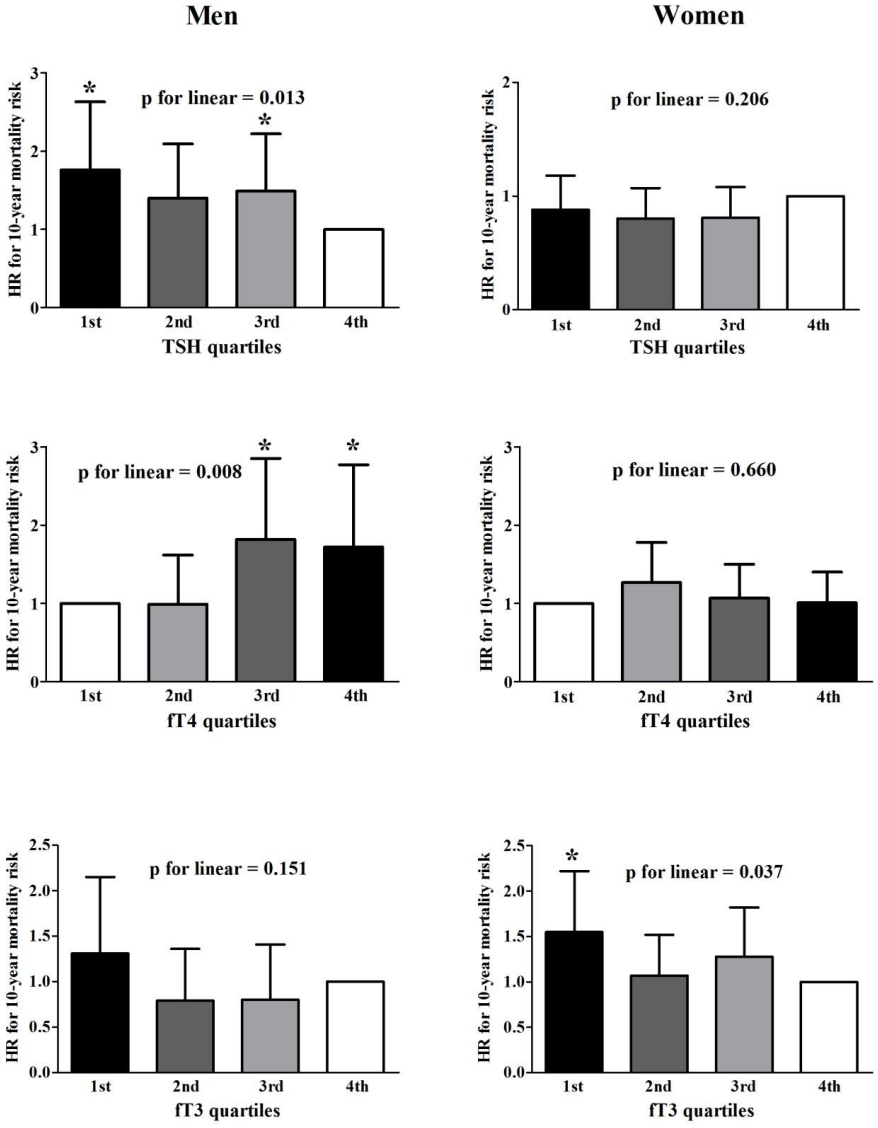
## Table 1. Characteristics of study population at baseline

| Characteristics | Quartiles of TSH (mU/L) | | | | | p-value |
|---|---|---|---|---|---|---|
| | All | First | Second | Third | Fourth | |
| | | 0.24-1.02 | 1.03-1.55 | 1.56-2.16 | 2.17-3.98 | |
| **Men** | n=338 | n=89 | n=89 | n=89 | n=71 | |
| Demographics, years, mean (SD) | | | | | | |
| Age | 81.6 (4.6) | 81.5 (4.3) | 81.2 (4.4) | 81.6 (4.8) | 82.3 (4.9) | 0.523 |
| Education | 9.8 (5.0) | 9.3 (4.6) | 9.6 (5.0) | 9.7 (5.2) | 11.2 (5.0) | 0.101 |
| Risk factors/ comorbidities, n (%) | | | | | | |
| Ever smoker | 228 (67.5) | 64 (71.9) | 61 (68.5) | 56 (62.9) | 47 (66.2) | 0.629 |
| Hypertension | 222 (65.7) | 62 (69.7) | 55 (61.8) | 57 (64.0) | 48 (67.6) | 0.695 |
| Diabetes mellitus | 53 (15.7) | 15 (16.9) | 16 (18.0) | 12 (13.5) | 10 (14.1) | 0.823 |
| Atrial fibrillation | 62 (18.3) | 9 (10.1) | 18 (20.2) | 19 (21.3) | 16 (22.5) | 0.132 |
| Coronary heart disease | 98 (29.0) | 26 (29.2) | 23 (25.8) | 26 (29.2) | 23 (32.4) | 0.842 |
| Claudication | 34 (10.1) | 13 (14.6) | 6 (6.7) | 10 (11.2) | 5 (7.0) | 0.265 |
| Depression or anxiety | 136 (40.2) | 46 (51.7) | 35 (39.3) | 30 (33.7) | 25 (35.2) | 0.066 |
| Stroke or TIA | 66 (19.5) | 19 (21.3) | 21 (23.6) | 15 (16.9) | 11 (15.5) | 0.519 |
| Cancer | 53 (15.7) | 15 (16.9) | 11 (12.4) | 15 (16.9) | 12 (16.9) | 0.799 |
| Heart failure | 35 (10.4) | 5 (5.6) | 11 (12.4) | 7 (7.9) | 12 (16.9) | 0.093 |
| N of drugs, mean (SD) | 3.8 (2.4) | 3.8 (2.5) | 3.7 (2.3) | 3.4 (2.4) | 4.1 (2.4) | 0.322 |
| fT4 (ng/L), mean (SD) | 12.0 (2.1) | 12.3 (2.2) | 12.1 (1.9) | 12.0 (1.9) | 11.4 (2.2) | 0.147 |
| fT3 (pg/mL), mean (SD) | 2.9 (0.5) | 2.9 (0.5) | 2.9 (0.6) | 2.9 (0.5) | 2.9 (0.6) | 0.995 |
| **Women** | n=630 | n=152 | n=152 | n=155 | n=171 | |
| Demographics, years, mean (SD) | | | | | | |
| Age | 82.2 (4.9) | 82.4 (4.6) | 82.2 (4.8) | 81.4 (5.2) | 82.8 (4.8) | 0.074 |
| Education | 6.9 (3.8) | 6.3 (3.3) | 7.2 (3.7) | 6.9 (3.8) | 7.3 (4.3) | 0.082 |
| Risk factors/ comorbidities, n (%) | | | | | | |
| Ever smoker | 146 (23.2) | 29 (19.1) | 33 (21.7) | 41 (26.5) | 43 (25.1) | 0.404 |
| Hypertension | 445 (70.6) | 113 (74.3) | 100 (65.8) | 109 (70.3) | 123 (71.9) | 0.412 |
| Diabetes mellitus | 74 (11.7) | 17 (11.2) | 17 (11.2) | 19 (12.3) | 21 (12.3) | 0.981 |
| Atrial fibrillation | 80 (12.7) | 13 (8.6) | 19 (12.5) | 21 (13.5) | 27 (15.8) | 0.268 |
| Coronary heart disease | 132 (21.0) | 33 (21.7) | 25 (16.4) | 29 (18.7) | 45 (26.3) | 0.148 |
| Claudication | 30 (4.8) | 7 (4.6) | 7 (4.6) | 4 (2.6) | 12 (7.0) | 0.313 |
| Depression or anxiety | 356 (56.5) | 80 (52.6) | 88 (57.9) | 94 (60.6) | 94 (55.0) | 0.514 |
| Stroke or TIA | 83 (13.2) | 13 (8.6) | 21 (13.8) | 14 (9.0) | 35 (20.5) | **0.004** |
| Cancer | 41 (6.5) | 7 (4.6) | 15 (9.9) | 7 (4.5) | 12 (7.0) | 0.186 |
| Heart failure | 50 (7.9) | 12 (7.9) | 14 (9.2) | 10 (6.5) | 14 (8.2) | 0.845 |
| N of drugs, mean (SD) | 3.5 (2.3) | 3.3 (2.2) | 3.4 (2.3) | 3.4 (2.3) | 3.9 (2.3) | 0.115 |
| fT4 (ng/L), mean (SD) | 12.3 (2.1) | 12.6 (1.9) | 12.3 (2.2) | 12.5 (2.3) | 11.8 (2.1) | **0.026** |
| fT3 (pg/mL), mean (SD) | 3.0 (0.5) | 2.9 (0.5) | 3.0 (0.5) | 3.0 (0.6) | 3.0 (0.6) | 0.456 |

P-values were calculated using ANOVA or chi-square test where appropriate. Abbreviations: SD: standard deviation, n: number, TSH: thyrotropin, fT4: free thyroxine, fT3: triiodothyronine, TIA: transient ischemic attack.

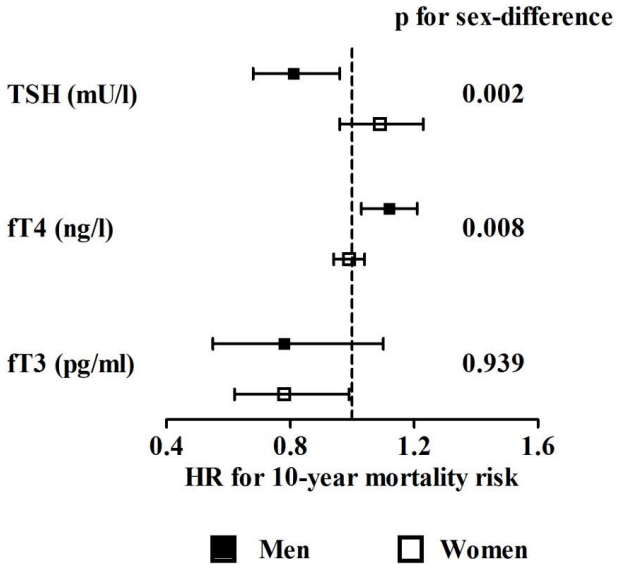
**Figure 1. Association of quartiles of TSH, fT4 and fT3 with 10-year mortality risk by sex**




Bars represent hazard ratios (95% confidence interval). The fourth TSH quartile, the first fT4 quartile and the fourth fT3 quartile were set as reference categories. The symbol * indicates a significant difference with the reference. P-values were computed using continuous TSH, fT4 and fT3. Analyses were adjusted for age, education, smoking, hypertension, diabetes mellitus, atrial fibrillation, CHD, claudication, heart failure, depression/anxiety, stroke/TIA, cancer, number of medications. Ranges for TSH quartiles are first: 0.24-1.02, second: 1.03-1.55, third: 1.56-2.16 and fourth: 2.17-3.98 mU/L. Ranges for fT4 quartiles are first: 8.1-10.6,

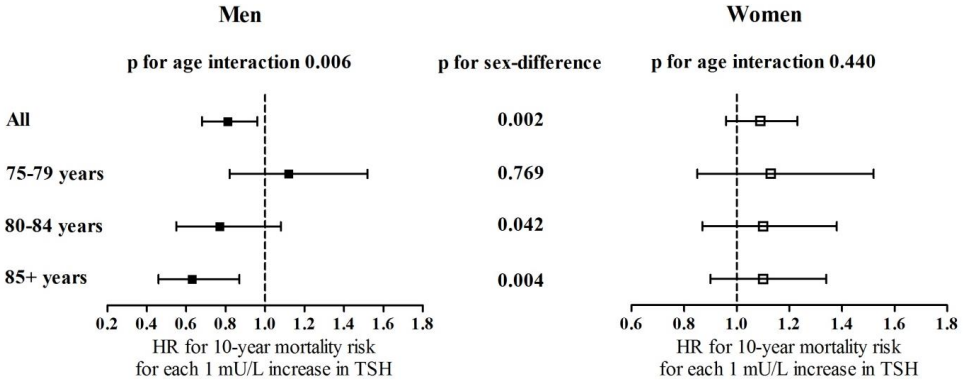
second: 10.7-11.9, third: 12.0-13.5 and fourth: 13.6-18.0 ng/L. Ranges for fT3 quartiles are first: 2.00-2.54, second: 2.55-2.90, third: 2.91-3.29 and fourth: 3.30-4.64 pg/mL. Abbreviations: HR: hazard ratio, TSH: thyrotropin, fT4: free thyroxine, fT3: triiodothyronine.

**Figure 2. Association of TSH, fT4 and fT3 with 10-year mortality risk by sex**



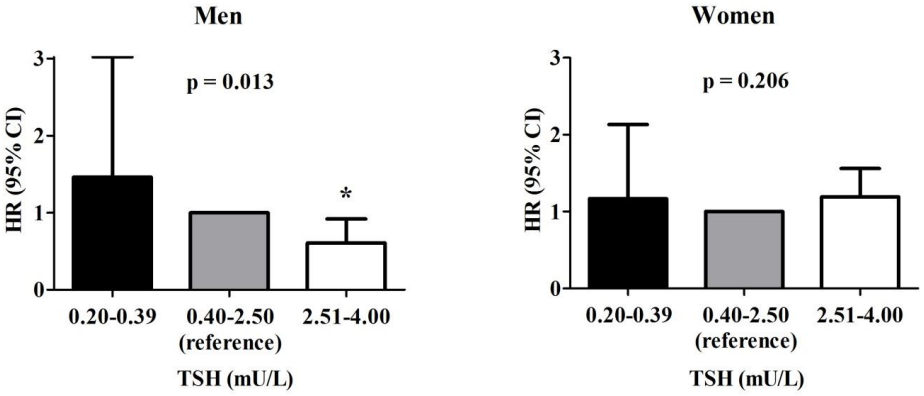

Bars represent hazard ratios (95% confidence interval) for 10-year mortality risk for each 1 mU/L increase in TSH, 1 ng/L increase in fT4 and 1 pg/mL increase in fT3. Analyses were adjusted for age, education, smoking, hypertension, diabetes mellitus, atrial fibrillation, CHD, claudication, heart failure, depression/anxiety, stroke/TIA, cancer, number of medications. Abbreviations: HR: hazard ratio, TSH: thyrotropin, fT4: free thyroxine, fT3: triiodothyronine.

**Figure 3. Association between TSH and 10-year mortality risk by sex and age**



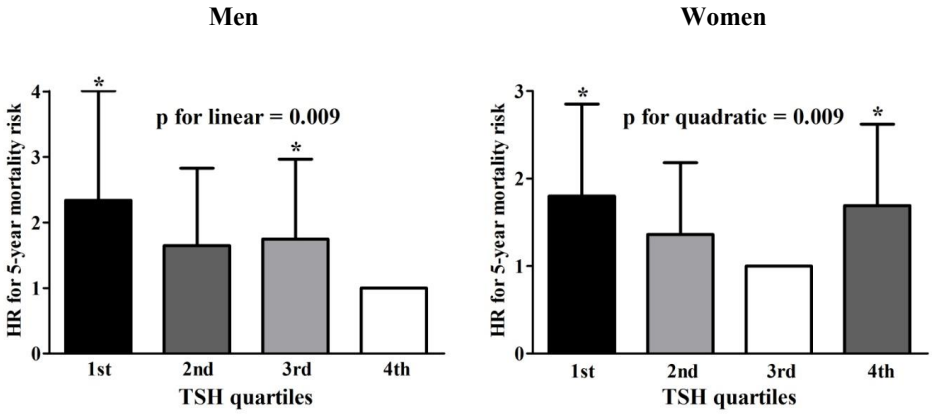

Bars represent hazard ratios (95% confidence interval). Analyses were adjusted for age, education, smoking, hypertension, diabetes mellitus, atrial fibrillation, CHD, claudication, heart failure, depression/anxiety, stroke/TIA, cancer, number of medications. P-values for age interaction were computed using TSH and age as continuous variables. Abbreviations: HR: hazard ratio, TSH: thyrotropin.

**Figure 4. Association between TSH categories and 10-year mortality risk by sex**




Bars represent hazard ratios (95% confidence interval). Analyses were adjusted for age, education, smoking, hypertension, diabetes mellitus, atrial fibrillation, CHD, claudication, heart failure, depression/anxiety, stroke/TIA, cancer, number of medications. Abbreviations: HR: hazard ratio, TSH: thyrotropin. The symbol * indicates a significant difference with the reference category. P-values were calculated for continuous TSH.

**Supplementary Figure 1. Association of quartiles of TSH with 5-year mortality risk by sex**




Bars represent hazard ratios (95% confidence interval). The fourth and the third TSH quartile were set as reference category for men and women, respectively. The symbol * indicates a significant difference with the reference. P-values for linear and for quadratic association were computed using TSH and squared TSH as continuous measures, respectively. Analyses were adjusted for age, education, smoking, hypertension, diabetes mellitus, atrial fibrillation, CHD, claudication, heart failure, depression/anxiety, stroke/TIA, cancer, number of medications. Ranges for TSH quartiles are first: 0.24-1.02, second: 1.03-1.55, third: 1.56-2.16 and fourth: 2.17-3.98 mU/L. Abbreviations: HR: hazard ratio, TSH: thyrotropin.

**Supplementary Table 1. Association of TSH, fT4 and fT3 with mortality risk at different follow-ups**

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | HR [95% CI] | p-value for linear | p-value for quadratic | HR [95% CI] | p-value for linear | p-value for quadratic |
| **TSH** | | | | | | |
| At 1-year | 0.61 [0.35; 1.07] | 0.086 | 0.695 | 0.77 [0.50; 1.18] | 0.227 | 0.099 |
| At 5-year | 0.74 [0.59; 0.93] | **0.009** | 0.818 | 1.05 [0.87; 1.25] | 0.630 | **0.009** |
| At 10-year | 0.81 [0.68; 0.96] | **0.013** | 0.977 | 1.09 [0.96; 1.23] | 0.206 | 0.074 |
| **fT4** | | | | | | |
| At 1-year | 1.08 [0.85; 1.38] | 0.508 | 0.100 | 1.03 [0.85; 1.24] | 0.766 | 0.335 |
| At 5-year | 1.12 [1.01; 1.24] | **0.033** | 0.390 | 0.99 [0.91; 1.07] | 0.775 | 0.622 |
| At 10-year | 1.12 [1.03; 1.21] | **0.008** | 0.521 | 0.99 [0.94; 1.04] | 0.660 | 0.909 |
| **fT3** | | | | | | |
| At 1-year | 0.50 [0.14; 1.79] | 0.287 | 0.600 | 0.45 [0.19; 1.09] | 0.077 | 0.461 |
| At 5-year | 0.62 [0.38; 1.00] | **0.050** | 0.321 | 0.59 [0.41; 0.84] | **0.004** | 0.930 |
| At 10-year | 0.78 [0.55; 1.10] | 0.151 | 0.931 | 0.78 [0.62; 0.99] | **0.037** | 0.827 |

Hazard ratios (95% confidence intervals) are for each 1 mU/L increase in TSH, 1 ng/L increase in fT4 and 1 pg/mL increase in fT3. All analyses were adjusted for age, education, smoking, hypertension, diabetes mellitus, atrial fibrillation, CHD, claudication, heart failure, depression/anxiety, stroke/TIA, cancer, number of medications. P-values for linear and quadratic associations were calculated using TSH, fT4 and fT3 as continuous variables in Cox-regression. Abbreviations: HR: hazard ratio, CI: confidence interval, TSH: thyrotropin, fT4: free thyroxine, fT3: triiodothyronine.