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Research Article

Thyroid Status and Mortality Risk in Older Adults With Normal Thyrotropin: Sex Differences in the Milan Geriatrics 75+ Cohort Study

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Abstract

Background: Thresholds of optimal thyroid status in old age are controversial. We investigated the longitudinal association between thyroid parameters and 10-year all-cause mortality risk in older outpatients with normal thyrotropin (TSH) and modification by sex and age.

Methods: Baseline TSH, free thyroxine (fT4), and free triiodothyronine (fT3) were assessed in the Milan Geriatrics 75+ Cohort Study. 324 men and 609 women older than 75 years had normal TSH. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for the associations between thyroid parameters and mortality risk using Cox regression. Sex-stratified analyses were adjusted for sociodemographic factors and comorbidities.

Results: 233 men and 367 women died during follow-up. After adjustment, each 1-mU/L higher TSH was associated with decreased mortality risk in men (HR 0.83, 95% CI 0.69–0.98), but not in women (HR 1.09, 95% CI 0.95–1.24) (p for sex interaction = .006). Each 1-ng/L higher fT4 was associated with increased mortality risk in men (HR 1.11, 95% CI 1.02–1.22), but not in women (HR 0.98, 95% CI 0.93–1.04) (p for sex interaction = .013). Each 1-pg/mL higher fT3 was associated with decreased mortality risk in women (HR 0.77, 95% CI 0.60–0.98), but not in men (HR 0.80, 95% CI 0.57–1.13). The inverse association between TSH and mortality was most pronounced in men older than 85 years.

Conclusions: Among older outpatients with normal TSH, 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.

Keywords: Longevity, Thyrotropin, Thyroxine, Geriatric cohort

Thresholds of optimal thyroid status in old age, particularly the normal thyrotropin (TSH) reference range, are 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 toward 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 higher TSH. Indeed, exceptionally long-lived adults and their offspring exhibit higher normal TSH with unchanged free thyroxine (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 free triiodothyronine (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 also ambiguous (12,15,19). Finally, most current evidence is from population-based studies comprising adults with wide age ranges, which limits their applicability to the oldest old adults. 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 associations between thyroid status and mortality risk in older men and women with normal TSH enrolled in the Milan Geriatrics 75+ Cohort Study, a longitudinal geriatric outpatient cohort. Furthermore, we investigated whether these associations differed by sex and age.

Methods

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 January 3, 2000 and March 25, 2004, 1,861 consecutive outpatients aged 75 years and older attended a first face-to-face, standardized, structured, comprehensive visit with trained physicians, after informed consent. The study has been described in detail previously (20).

To explore the association between thyroid parameters and mortality, unmodified by thyroid disease and medical intervention, we excluded participants with known thyroid disease, defined as a clinical diagnosis or current use of thyroid hormone or antithyroid medication (n = 86), those taking medications potentially affecting thyroid parameters (amiodar or lithium, n = 39), those with missing data on mortality (n = 51), and those with baseline TSH less than 0.20 mU/L or more than 4.00 mU/L (n = 130) or missing TSH (n = 622). Therefore, we included 933 participants with normal TSH in the present analysis. Of these participants, 291 (31.2%) had originally been referred to the Geriatric Unit for global evaluation, 303 (32.5%) for cognitive evaluation, and 339 (36.3%) for other reasons.

Data on fT4 and fT3 were available for 730 and 679 participants, respectively; analyses were performed in 709 and 628 participants, that is, those with fT4 and fT3 within the reference range. The I.R.C.C.S. Ca' Granda Ethics Committee approved the study.

Thyroid Parameters

Blood for baseline measurements was drawn in the morning, after an overnight fast. Serum TSH, fT4, and fT3 were measured using chemiluminescent assays (Immulite2000, 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.

Comorbidities and Lifestyle Factors

A geriatrician examined each participant's record. Baseline data on 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 5 years. Symptoms of anxiety/depression were self-reported or stated in medical documents. Smoking was dichotomized as never versus ever. 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 or loss to follow-up, or 10 years.

Statistical Analyses

Differences in baseline characteristics between sexes and across TSH quartiles were assessed using Student's t test, one-way analysis of variance, or chi-square test where appropriate.

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 nonlinear associations, by entering thyroid parameters and squared thyroid parameters in the Cox regression as continuous variables.

To explore sex interaction in the relationship between thyroid parameters and mortality risk, we computed interaction terms by multiplying continuous thyroid parameters 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 interaction by sex within age strata.

As a sensitivity analysis, we repeated all analyses in solely euthyroid participants, defined as having both TSH and fT4 levels within the reference range. Further analyses were run using three categories of TSH values, defined according to clinical cutoffs (0.20–0.39, 0.40–2.50, 2.51–4.00 mU/L) (2,21).

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, 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), 609 (65.3%) participants were women, and 926 (99.2%) were Caucasians. Mean TSH, fT4, and fT3 were 1.68 mU/L, 12.2 ng/L, and 2.9 pg/mL, respectively. Mean TSH and fT3 did not differ by sex (both p values > .05), whereas mean fT4 was lower in men than in women (11.9 versus 12.3 ng/L, p = .021). Men were younger, more educated, and more likely to be smokers and to have atrial fibrillation, CHD, claudication, stroke/TIA, or cancer, but less likely to have depression/anxiety compared with women (all p values < .05).

fT4 was inversely associated with the logarithm of TSH in men (β = −0.018, 95% CI −0.034 to −0.002, p = .026) and women

Table 1. Characteristics of Study Population at Baseline

Characteristics	All	Quartiles of TSH (mU/L) First 0.24–1.02	Second 1.03–1.54	Third 1.55–2.15	Fourth 2.16–3.98	*p* Value
Men	*n* = 324	*n* = 85	*n* = 84	*n* = 89	*n* = 66	
Demographics, years, mean (*SD*)						
Age	81.6 (4.6)	81.3 (4.3)	81.4 (4.5)	81.4 (4.7)	82.3 (5.0)	.553
Education	10.0 (5.0)	9.4 (4.7)	9.5 (5.0)	10.0 (5.3)	11.4 (4.9)	.070
Risk factors/comorbidities, *n* (%)						
Ever smoker	219 (67.6)	62 (72.9)	58 (69.0)	55 (61.8)	44 (66.7)	.461
Hypertension	213 (65.7)	60 (70.6)	53 (63.1)	57 (64.0)	43 (65.2)	.736
Diabetes mellitus	52 (16.0)	15 (17.6)	16 (19.0)	12 (13.5)	9 (13.6)	.696
Atrial fibrillation	55 (17.0)	6 (7.1)	17 (20.2)	18 (20.2)	14 (21.2)	**.045**
Coronary heart disease	90 (27.8)	25 (29.4)	21 (25.0)	25 (28.1)	19 (28.8)	.925
Claudication	33 (10.2)	13 (15.3)	5 (6.0)	10 (11.2)	5 (7.6)	.198
Depression/anxiety	131 (40.4)	44 (51.8)	33 (39.3)	31 (34.8)	23 (34.8)	.086
Stroke/TIA	64 (19.8)	18 (21.2)	19 (22.6)	16 (18.0)	11 (16.7)	.773
Cancer	52 (16.0)	15 (17.6)	11 (13.1)	15 (16.9)	11 (16.7)	.857
Heart failure	29 (9.0)	4 (4.7)	10 (11.9)	6 (6.7)	9 (13.6)	.165
Number of drugs, mean (*SD*)	3.7 (2.4)	3.8 (2.5)	3.7 (2.3)	3.3 (2.3)	3.9 (2.3)	.422
fT4 (ng/L), mean (*SD*)	11.9 (2.0)	12.2 (2.1)	12.0 (1.8)	12.0 (2.0)	11.2 (2.1)	.086
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)	.982
Women	*n* = 609	*n* = 148	*n* = 147	*n* = 148	*n* = 166	
Demographics, years, mean (*SD*)						
Age	82.3 (4.9)	82.4 (4.6)	82.2 (4.9)	81.4 (5.2)	82.9 (4.8)	.051
Education	7.0 (3.8)	6.3 (3.3)	7.2 (3.8)	6.9 (3.9)	7.4 (4.3)	.079
Risk factors/comorbidities, *n* (%)						
Ever smoker	136 (22.3)	27 (18.2)	31 (21.1)	39 (26.4)	39 (23.5)	.382
Hypertension	430 (70.6)	110 (74.3)	97 (66.0)	103 (69.6)	120 (72.3)	.424
Diabetes mellitus	71 (11.7)	17 (11.5)	17 (11.6)	18 (12.2)	19 (11.4)	.997
Atrial fibrillation	71 (11.7)	11 (7.4)	17 (11.6)	19 (12.8)	24 (14.5)	.258
Coronary heart disease	126 (20.7)	32 (21.6)	23 (15.6)	26 (17.6)	45 (27.1)	.060
Claudication	30 (4.9)	7 (4.7)	7 (4.8)	4 (2.7)	12 (7.2)	.326
Depression/anxiety	341 (56.0)	78 (52.7)	87 (59.2)	86 (58.1)	90 (54.2)	.628
Stroke/TIA	80 (13.1)	13 (8.8)	21 (14.3)	12 (8.1)	34 (20.5)	**.003**
Cancer	40 (6.6)	7 (4.7)	15 (10.2)	6 (4.1)	12 (7.2)	.131
Heart failure	48 (7.9)	12 (8.1)	14 (9.5)	9 (6.1)	13 (7.8)	.749
Number of drugs, mean (*SD*)	3.5 (2.3)	3.3 (2.2)	3.4 (2.3)	3.4 (2.3)	3.9 (2.3)	.096
fT4 (ng/L), mean (*SD*)	12.3 (2.1)	12.6 (1.9)	12.3 (2.1)	12.5 (2.3)	11.8 (2.0)	**.017**
fT3 (pg/mL), mean (*SD*)	3.0 (0.5)	2.9 (0.5)	3.0 (0.5)	3.0 (0.5)	3.0 (0.6)	.681

Notes: p Values were calculated using analysis of variance or chi-square test. Bold values indicate that *p* Values less than .05 were considered as significant. fT3 = triiodothyronine; fT4 = free thyroxine; TIA = transient ischemic attack; TSH = thyrotropin.

(β = –0.014, 95% CI –0.025 to –0.004, $p = .007$), as shown in previous literature (22).

After 10-year follow-up, 233 (71.9%) men and 367 (60.3%) 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 < .05; Figure 1). At 10-year follow-up, no U-shaped associations were observed (all *p* values for quadratic associations > .05).

In contrast, the association between TSH and 5-year mortality risk in women was U shaped, also after full adjustment (*p* value for quadratic association = .005; 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 0.83-fold (95% CI 0.69–0.98, $p = .030$) decreased mortality risk in men, but not in women (HR 1.09, 95% CI 0.95–1.24, $p = .210$) (*p* for sex difference = .006). Likewise, each 1-ng/L higher fT4 was associated with a 1.11-fold (95% CI 1.02–1.22, $p = .015$) increased mortality risk in men, but not in women (HR 0.98, 95% CI 0.93–1.04, $p = .526$) (*p* for sex difference = .013). Each 1-pg/mL higher fT3 was associated with decreased mortality risk in women (HR 0.77, 95% CI 0.60–0.98, $p = .035$), whereas the association was not significant in men (*p* for sex difference = .884).

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 0.85-fold (95% CI 0.60–1.20, $p = .344$) and with a 0.62-fold (95% CI 0.44–0.87, $p = .006$) decreased mortality risk in men aged 80–84 years and 85 years and older, respectively. In contrast, the association tended to reverse in men aged 75–79 years (HR 1.05, 95% CI 0.76–1.44, $p = .782$). In men, interaction by age was significant ($p = .012$). In women, we observed neither an association between TSH and mortality risk in any age strata nor interaction by age.

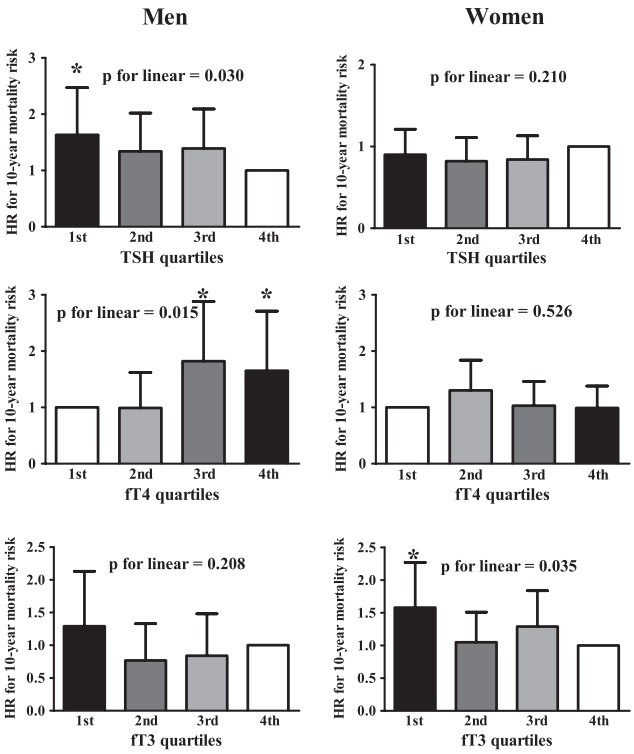

Figure 1. Association of quartiles of thyrotropin (TSH), free thyroxine (fT4), and free triiodothyronine (fT3) with 10-year mortality risk by sex. Bars represent hazard ratios (95% confidence interval). The fourth TSH quartile, the first fT4 quartile, and the fourth fT3 quartile were set as references. The symbol "*" indicates a significant difference with the reference. *p* Values were computed using continuous TSH, fT4, and fT3. Analyses were fully adjusted.

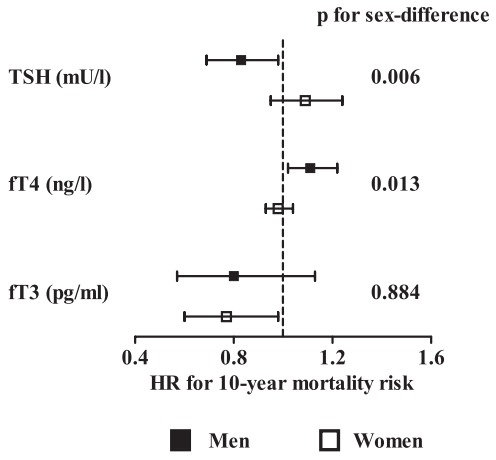

Figure 2. Association of thyrotropin (TSH), free thyroxine (fT4), and free triiodothyronine (fT3) with 10-year mortality risk by sex. Bars represent hazard ratios (95% confidence interval) for 10-year mortality risk for each 1-mU/L increase in TSH, 1-ng/L increase in fT4, and 1-pg/mL increase in fT3. Analyses were fully adjusted.

Sex differences in the relationship between TSH and mortality risk were not present in participants aged 75–79 years or 80–84 years (both *p* values > .05), whereas they appeared in those aged 85 years and older ($p = .006$) (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* values > .05, data not shown).

Further adjusting for fT3, a marker responsive to underlying stressors (eg, inflammatory processes), did not markedly change the association of TSH and fT4 with 10-year mortality risk (data not shown).

Furthermore, when the analyses were restricted to euthyroid participants (ie, those with both TSH and fT4 in the reference range), the association between TSH and mortality risk remained similar (Supplementary Table 2). After full adjustment, euthyroid men with TSH 2.51–4.00 mU/L had a 0.52-fold (95% CI 0.30–0.89, $p = .018$) decreased 10-year mortality risk compared with those with TSH 0.40–2.50 mU/L (Supplementary Figure 2).

We tested differences in baseline characteristics between participants excluded from the analyses due to missing TSH and those included. Included men were more likely to be smokers, compared with those excluded; included women were younger, less educated, more likely to be smokers, to have depression/anxiety and to use more medications, compared with those excluded. We checked whether the associations of TSH, fT4, and fT3 with mortality risk might differ in relation to smoking, depression/anxiety, education, and number of medications by testing for interaction. No interaction was observed (all *p* values > .05).

Discussion

Among older outpatients with normal TSH, higher TSH and lower fT4 were associated with decreased mortality risk in men, but not in women. The inverse association between TSH and mortality risk was most pronounced in men aged 85 years and older. 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), though 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 interaction by sex in the relationship between TSH and mortality risk, especially in participants aged 85 years and older. Consistent with this, the Leiden 85+ Study reported an inverse association between TSH and mortality risk in men, but not in women, without formally checking for sex interaction (16). Other studies failed to show sex interaction for all-cause mortality in populations younger than ours (12,18). Sex modified the association between TSH and cardiovascular-specific mortality in a middle-aged cohort; higher TSH was associated with increased cardiovascular-specific mortality in women, but not in men (11). Our observation that lower fT4 was associated with decreased mortality risk in men is in line with a study comprising nearly 4,000 older men (23).

Why does sex modify the relationship between thyroid status and mortality? First, women compared with men have higher prevalence and incidence of subclinical and overt thyroid dysfunctions, which have been associated with an excess of mortality (24). 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 (25). Women live longer than men do, by surviving diseases that are fatal in men (25).

High normal thyroid status, as characterized by lower TSH and higher fT4 within the reference range, has been linked to adverse health outcomes (10). These may result from different

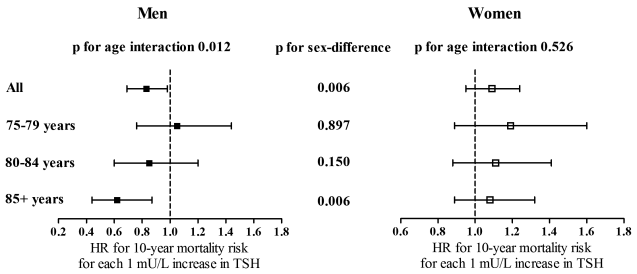

Figure 3. Association between thyrotropin (TSH) and 10-year mortality risk by sex and age. Bars represent hazard ratios (95% confidence interval). Analyses were fully adjusted. *p* Values for age interaction were computed using TSH and age as continuous variables.

pathophysiological mechanisms, including increased metabolic rate and altered cardiovascular hemodynamics (26). 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 (21,27,28). Higher fT4 has also been directly related to frailty in euthyroid community-dwelling older men (19,29).

Furthermore, high normal thyroid status may affect brain structure and function. High thyroid status may favor thromboembolism and brain vascular damage through a combination of atrial fibrillation, endothelial dysfunction, and hypercoagulability (24). Alternatively, it may directly cause neurodegeneration through increased oxidative stress (24). However, controversy persists on the association between thyroid status and cognitive impairment and dementia, which, in turn, have been associated with increased mortality risk (30–33).

High normal thyroid status may be particularly detrimental in older adults with cardiovascular comorbidities (26). 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 with women. However, sex interaction 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 toward higher TSH values in adults with genetic predisposition to longevity (6). Men older than 85 years in our study had above-average life expectancy, thus suggesting a genetic longevity trait (34). Animal studies have suggested a causal relationship between lower thyroid status and extended life span (35). 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 (35). Other mechanisms may include effects on membrane composition, inflammation, and stem cell renewal (36).

Our finding of an association between lower fT3 and increased mortality risk is in line with The Aging in the Chianti Area Study (15). Lower fT3 in euthyroid older individuals may be indicative of nonthyroidal systemic illnesses (15,37,38).

Indeed, low normal TSH, especially in conjunction with low fT3, may be indicative of underlying stresses, like inflammation (37,38). However, in our study, the associations of TSH and fT4 with mortality did not markedly change after adjusting for fT3, and are thus likely independent of fT3 or conditions marked by low fT3.

In our study, age modified the association between TSH and mortality, but not the association between fT4 and mortality. This may imply distinct associations of TSH with mortality, compared with those of fT4. Indeed, other cells than those of the thyroid gland express functional TSH receptors, and extrathyroidal effects of TSH have been implicated in mechanisms that are relevant to old age mortality (39).

Our study has relevant clinical implications. First, our findings suggest that clinicians should take sex and age into account when assessing thyroid status. Furthermore, we found that older euthyroid men with TSH 2.51–4.00 mU/L had a 0.52-fold decreased mortality risk compared with those with TSH 0.40–2.50 mU/L. This observational finding conflicts with the proposed lowering of TSH upper reference limit, at least in older men (2).

A major strength of our study is our unselected population of older geriatric outpatients, which makes our findings generalizable in common clinical practice, whereas clinical trials recruit few or selected older adults (40). A further asset is the longitudinal design, with a long follow-up. However, the observational nature of our study limits us in inferring causality. Another limitation may be our exclusion of participants with missing TSH. However, baseline differences between included and excluded participants were not likely to distort our associations, given the absence of interaction and the adjustment for these baseline covariates. Furthermore, a single measurement of thyroid status was used, potentially leading to misclassification of participants. However, intra-individual variability of thyroid status is narrow and less than inter-individual variability (8). Moreover, random misclassification would merely underestimate 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 replicate our findings on sex interaction in old populations and to establish whether the relationship between thyroid status and mortality is causal.

Supplementary Material

Please visit the article online at http://gerontologist.oxfordjournals.org/ to view supplementary material.

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References

1. Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. *Thyroid*. 2014;24:1670–1751. doi:10.1089/thy.2014.0028
2. Pearce SH, Brabant G, Duntas LH, et al. 2013 ETA Guideline: Management of subclinical hypothyroidism. *Eur Thyroid J*. 2013;2:215–228. doi:10.1159/000356507
3. Laurberg P, Andersen S, Carlé A, Karmisholt J, Knudsen N, Pedersen IB. The TSH upper reference limit: where are we at? *Nat Rev Endocrinol*. 2011;7:232–239. doi:10.1038/nrendo.2011.13
4. Surks MI, Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. *J Clin Endocrinol Metab*. 2007;92:4575–4582.
5. Åsvold BO, Vatten LJ, Midthjell K, Bjøro T. Serum TSH within the reference range as a predictor of future hypothyroidism and hyperthyroid-

ism: 11-year follow-up of the HUNT Study in Norway. *J Clin Endocrinol Metab*. 2012;97:93–99. doi:10.1210/jc.2011-1724
6. Atzmon G, Barzilai N, Surks MI, Gabriely I. Genetic predisposition to elevated serum thyrotropin is associated with exceptional longevity. *J Clin Endocrinol Metab*. 2009;94:4768–4775. doi:10.1210/jc.2009-0808
7. Hansen PS, Brix TH, Sørensen TI, Kyvik KO, Hegedüs L. Major genetic influence on the regulation of the pituitary-thyroid axis: a study of healthy Danish twins. *J Clin Endocrinol Metab*. 2004;89:1181–1187.
8. Andersen S, Pedersen KM, Bruun NH, Laurberg P. Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease. *J Clin Endocrinol Metab*. 2002;87:1068–1072.
9. Porcu E, Medici M, Pistis G, et al. A meta-analysis of thyroid-related traits reveals novel loci and gender-specific differences in the regulation of thyroid function. *PLoS Genet*. 2013;9:e1003266. doi:10.1371/journal.pgen.1003266
10. Taylor PN, Razvi S, Pearce SH, Dayan CM. Clinical review: A review of the clinical consequences of variation in thyroid function within the reference range. *J Clin Endocrinol Metab*. 2013;98:3562–3571. doi:10.1210/jc.2013-1315
11. Asvold BO, Bjoro T, Nilsen TI, Gunnell D, Vatten LJ. Thyrotropin levels and risk of fatal coronary heart disease: the HUNT Study. *Arch Intern Med*. 2008;168:855–860. doi:10.1001/archinte.168.8.855
12. Zhang Y, Chang Y, Ryu S, et al. Thyroid hormones and mortality risk in euthyroid individuals: the Kangbuk Samsung health study. *J Clin Endocrinol Metab*. 2014;99:2467–2476. doi:10.1210/jc.2013-3832
13. Ittermann T, Haring R, Sauer S, et al. Decreased serum TSH levels are not associated with mortality in the adult northeast German population. *Eur J Endocrinol*. 2010;162:579–585. doi:10.1530/EJE-09-0566
14. Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA. Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. *Lancet*. 2001;358:861–865.
15. Ceresini G, Ceda GP, Lauretani F, et al. Thyroid status and 6-year mortality in elderly people living in a mildly iodine-deficient area: the aging in the Chianti Area Study. *J Am Geriatr Soc*. 2013;61:868–874. doi:10.1111/jgs.12267
16. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frölich M, Westendorp RG. Thyroid status, disability and cognitive function, and survival in old age. *JAMA*. 2004;292:2591–2599.
17. Pereg D, Tirosh A, Elis A, et al. Mortality and coronary heart disease in euthyroid patients. *Am J Med*. 2012;125:826 e827–e812. doi:10.1016/j.amjmed.2011.11.023
18. Cappola AR, Arnold AM, Wulczyn K, Carlson M, Robbins J, Psaty BM. Thyroid function in the euthyroid range and adverse outcomes in older adults. *J Clin Endocrinol Metab*. 2015;100:1088–1096. doi:10.1210/jc.2014-3586
19. van den Beld AW, Visser TJ, Feelders RA, Grobbee DE, Lamberts SW. Thyroid hormone concentrations, disease, physical function, and mortality in elderly men. *J Clin Endocrinol Metab*. 2005;90:6403–6409.
20. Ogliari G, Sabayan B, Mari D, et al. Age- and functional status-dependent association between blood pressure and cognition: the Milan Geriatrics 75+ Cohort Study. *J Am Geriatr Soc*. 2015;63:1741–1748. doi:10.1111/jgs.13616
21. Selmer C, Olesen JB, Hansen ML, et al. The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. *BMJ*. 2012;345:e7895. doi:10.1136/bmj.e7895
22. Spencer CA, LoPresti JS, Patel A, et al. Applications of a new chemiluminometric thyrotropin assay to subnormal measurement. *J Clin Endocrinol Metab*. 1990;70:453–460.
23. Yeap BB, Alfonso H, Hankey GJ, et al. Higher free thyroxine levels are associated with all-cause mortality in euthyroid older men: the Health In Men Study. *Eur J Endocrinol*. 2013;169:401–408. doi:10.1530/EJE-13-0306
24. Cooper DS, Biondi B. Subclinical thyroid disease. *Lancet*. 2012;379:1142–1154. doi:10.1016/S0140-6736(11)60276-6
25. Hubbard RE, Rockwood K. Frailty in older women. *Maturitas*. 2011;69:203–207. doi:10.1016/j.maturitas.2011.04.006
26. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. *N Engl J Med*. 2001;344:501–509.
27. Palatini P, Benetos A, Julius S. Impact of increased heart rate on clinical outcomes in hypertension: implications for antihypertensive drug therapy. *Drugs*. 2006;66:133–144.
28. Ogliari G, Mahinrad S, Stott DJ, et al. Resting heart rate, heart rate variability and functional decline in old age. *CMAJ*. 2015;187:E442-9. doi:10.1503/cmaj.150462
29. Yeap BB, Alfonso H, Chubb SA, et al. Higher free thyroxine levels are associated with frailty in older men: the Health In Men Study. *Clin Endocrinol*. 2012;76:741–748. doi:10.1111/j.1365-2265.2011.04290.x
30. Tan ZS, Beiser A, Vasan RS, et al. Thyroid function and the risk of Alzheimer disease: the Framingham Study. *Arch Intern Med*. 2008;168:1514–1520. doi:10.1001/archinte.168.14.1514
31. de Jong FJ, Masaki K, Chen H, et al. Thyroid function, the risk of dementia and neuropathologic changes: the Honolulu-Asia aging study. *Neurobiol Aging*. 2009;30:600–606.
32. Yeap BB, Alfonso H, Chubb SA, et al. Higher free thyroxine levels predict increased incidence of dementia in older men: the Health in Men Study. *J Clin Endocrinol Metab*. 2012;97:E2230–E2237. doi:10.1210/jc.2012-2108
33. World Health Organization and Alzheimer's Disease International. *Dementia: A Public Health Priority*, 2012 [Online]. http://www.who.int/mental_health/publications/dementia_report_2012/en. Accessed October 27, 2015.
34. Franceschi C, Motta L, Valensin S, et al. Do men and women follow different trajectories to reach extreme longevity? Italian Multicenter Study on Centenarians (IMUSCE). *Aging*. 2000;12:77–84.
35. Buffenstein R, Pinto M. Endocrine function in naturally long-living small mammals. *Mol Cell Endocrinol*. 2009;299:101–111. doi:10.1016/j.mce.2008.04.021
36. Bowers J, Terrien J, Clerget-Froidevaux MS, et al. Thyroid hormone signaling and homeostasis during aging. *Endocr Rev*. 2013;34:556–589. doi:10.1210/er.2012-1056
37. Adler SM, Wartofsky L. The nonthyroidal illness syndrome. *Endocrinol Metab Clin North Am*. 2007;36:657–672.
38. Straub RH. Interaction of the endocrine system with inflammation: a function of energy and volume regulation. *Arthritis Res Ther*. 2014;16:203. doi:10.1186/ar4484
39. Williams GR. Extrathyroidal expression of TSH receptor. *Ann Endocrinol*. 2011;72:68–73. doi:10.1016/j.ando.2011.03.006
40. Villar HC, Saconato H, Valente O, Atallah AN. Thyroid hormone replacement for subclinical hypothyroidism. *Cochrane Database Syst Rev*. 2007;3:CD003419.