CLINICAL STUDY

Decreased serum TSH levels are not associated with mortality in the adult northeast German population

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Abstract

Objective: Results of cohort studies on the association between decreased serum TSH levels and mortality are conflicting. Some studies demonstrated an increased mortality risk in subjects with decreased serum TSH levels, others did not. Even meta-analyses revealed contradictory results. We undertook the present study to investigate the association between decreased serum TSH levels and mortality in the large population-based Study of Health in Pomerania (SHIP).

Design and methods: Data from 3651 individuals from SHIP without known thyroid disorders or thyroid treatment were analyzed. Serum TSH, free triiodothyronine, and free thyroxine levels were determined by immunochemiluminescent procedures. Decreased TSH was defined as serum TSH levels below 0.25 mIU/l. Cox regression was used to associate decreased TSH levels with mortality.

Results: The median duration of follow-up was 8.5 years (30 126 person years). During follow-up, 299 individuals (6.9%) died corresponding to a death rate of 9.92 deaths per 1000 person years. Survival time was shorter in subjects with decreased serum TSH levels compared to euthyroid individuals. After adjustment for age and sex, however, there was no association between decreased serum TSH levels and all-cause mortality (hazard ratio: 0.95; 95% confidence interval: 0.67; 1.36). Likewise, decreased serum TSH levels were neither associated with cardiovascular nor with cancer mortality.

Conclusions: There is no independent association of decreased serum TSH levels with all-cause, cardiovascular, and cancer mortality in the adult northeast German population. Although our study has some strengths, we cannot finally conclude on therapeutical implications in individuals with subclinical thyroid diseases.

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Introduction

An association between decreased serum thyrotropin (TSH) levels and increased mortality may be explained by several mechanisms. Thus, decreased serum TSH levels have been reported to be associated with surrogate markers of cardiovascular mortality including carotid wall thickness (1), atrial fibrillation (2, 3), high plasma fibrinogen levels (4), and left ventricular hypertrophy (5, 6). However, results of studies on the association between decreased serum TSH levels or subclinical hyperthyroidism (3, 7–18) and mortality are conflicting. With respect to cardiovascular mortality, most studies (3, 11, 12, 18) and all meta-analyses (10, 14, 17) detected no association between decreased serum TSH levels or hyperthyroidism and mortality, while two studies did detect an association (7, 9). Regarding all-cause mortality, one study (7) demonstrated an increased mortality risk in subjects with decreased serum TSH levels, whereas two others did not

(12, 16). Focusing on subclinical hyperthyroidism, four studies (3, 9, 15, 18) did not detect an association with all-cause mortality, while one study in geriatric patients (13) did. With respect to overt hyperthyroidism, one study detected a relationship to all-cause mortality (11). Different results have occurred because of nonconsideration of major confounders in some studies (7, 11, 12), differences in definition of hyperthyroidism or follow-up time, and choice of the study population. Furthermore, some previous studies did not distinguish between subclinical and overt hyperthyroidism (7, 9, 12). The controversy on the association between hyperthyroidism and mortality is currently fostered because even meta-analyses revealed contradictory results. While one meta-analysis demonstrated an increased mortality risk in subjects with decreased serum TSH levels (8), three others did not confirm this finding (10, 14, 17).

With respect to cancer mortality, all available studies (19–24) compared participants after radioiodine treatment with a healthy reference group. Among these

studies, three detected a positive (21, 22, 24), one an inverse (20), and two (19, 23) no association of hyperthyroidism with cancer mortality.

In summary, current evidence for an association of decreased serum TSH levels with increased mortality is weak and nonconsistent (10, 14, 17). Thus, we investigated the association between decreased serum TSH levels and mortality in the large population-based Study of Health in Pomerania (SHIP) distinguishing between subclinical hyperthyroidism and overt hyperthyroidism.

Materials and methods

Study population

SHIP is a population-based cohort study in West Pomerania, a region in the northeast of Germany. Details on the study design have been published previously (1, 25). In brief, the total population of West Pomerania comprised 212 157 inhabitants. As in most parts of Germany, West Pomerania is a region of former iodine deficiency. During the 1990s, improved iodine supplementation has normalized this deficiency level resulting in a median iodine excretion value of 124 µg/l (26). For SHIP, a sample of the population aged 20–79 years was drawn from population registries. The net sample (without migrated or deceased persons) comprised 6267 eligible subjects. SHIP finally included 4310 participants (2193 women) corresponding to a final response of 68.8% (25). Baseline examinations were conducted between 1997 and 2001. All participants gave informed written consent. The study followed the recommendations of the Declaration of Helsinki and was approved by the Ethics Committee of the University of Greifswald.

Of the 4310 subjects who participated in SHIP, 162 subjects (76 women) had missing data in any of the considered variables, 323 subjects (272 women) reported a known thyroid disorder, 70 subjects (51 women) received thyroid treatment, and 104 subjects (68 women) had serum TSH levels above 2.12 mIU/l. These 659 participants (467 women) were excluded from further analysis resulting in a population of 3651 subjects (1726 women) who were available for the present analysis.

Assessments

Socio-demographic characteristics, history of smoking, known thyroid diseases, use of anti-thyroid treatment, history of myocardial infarction, stroke, and diabetes were assessed by computer-assisted personal interviews. Smokers were categorized into three categories (lifetime nonsmokers, former smokers, and current smokers). Former smokers were individuals who had smoked during their lifetime but not in the last 12 months prior to the time of examination. Height and weight were measured

for the calculation of the body mass index (BMI) = weight (kg)/height² (m²). After a 5 min rest period, systolic and diastolic blood pressure were measured three times at the right arm of seated subjects using a digital blood pressure monitor (HEM-705CP, Omron Corporation, Tokyo, Japan) with each reading being followed by a further rest period of 3 min. The mean of the second and third measurements was calculated and used for the present analyses. Hypertension was defined as increased systolic (≥ 140 mmHg), diastolic blood pressure (≥ 90 mmHg), or use of anti-hypertensive medication.

Blood samples were taken in supine position between 0700 and 1600 h, and were analyzed in the core laboratory of the University Hospital Greifswald. TSH, free triiodothyronine (FT₃), and free thyroxine (FT₄) levels were measured by immunochemiluminescent procedures (FT₃ LUMitest, Brahms, Berlin, Germany; TSH and FT₄ LIA-mat, Byk Sangtec Diagnostica GmbH, Frankfurt, Germany). The functional sensitivity of the TSH assay was 0.03 mIU/l. The reference range recently established for the SHIP region was 0.25–2.12 mIU/l (27). For determination of this reference range, all participants with a known thyroid disease, thyroid medication, goiter, inhomogeneous or hypoechogenic thyroid echo pattern, at least one thyroid nodule, or positive serum anti-thyroperoxidase (TPO) antibodies were excluded. Decreased TSH was defined using the lower reference level as cutoff. Subclinical hyperthyroidism was defined as serum TSH <0.25 mIU/l and FT₃ and FT₄ below the respective upper reference limit (FT₃ ≤ 7.0 pmol/l and FT₄ ≤ 18.9 pmol/l) (27). Overt hyperthyroidism was defined as serum TSH levels <0.25 mIU/l and FT₃ or FT₄ above the upper respective reference limit (FT₃ >7.0 pmol/l or FT₄ >18.9 pmol/l). For analysis regarding TSH in the reference range (0.25–2.12 mIU/l), groups were separated by quintiles. Serum cholesterol was measured enzymatically on a Hitachi 717 (Roche). Plasma fibrinogen concentrations were assayed according to Clauss (28) (Electra analyzer, Instrumentation Laboratory, Barcelona, Spain).

Information on vital status was collected at regular intervals from the time of enrolment into the study through August 31, 2007. Subjects were censored at death or loss to follow-up. The number of months between baseline examination and censoring was used as the follow-up length. The median duration of follow-up was 8.5 years (25th, 7.8; 75th, 9.2). During the 30 126 person years of follow-up, 299 participants (217 men) had died. During the 13 913 person years of follow-up, 299 participants (217 men) had died. Death certificates were requested from the local health authority at the place of death, and coded by a certified nosologist according to the International Classification of Diseases, 10th revision (ICD10). Two internists (H W and M D) independently validated the underlying cause of death, and performed a joint reading together with a third internist (H V) in cases of disagreement.

Statistical analysis

Data on quantitative characteristics are expressed as median and interquartile range. Data on qualitative characteristics are expressed as percent values or absolute numbers, as indicated. The study population was divided into two groups according to decreased serum TSH levels at baseline. Comparisons between groups were made using χ^2 -test (qualitative data) or Wilcoxon test (quantitative data). To assess the association between decreased serum TSH levels and mortality, we used Cox proportional hazards regression models with survival in years as dependent variable. Three different regression models were applied. The first crude, the second adjusted for age and sex, and the third additionally adjusted for smoking status, BMI, hypertension, myocardial infarction, stroke, cholesterol, diabetes, and fibrinogen. Additionally, interaction terms of decreased TSH with all covariates were added to the full model. All interactions with a value of $P < 0.1$ were retained. The model assumption for the Cox proportional hazards regression models was checked by visual inspection of proportional hazard assumption and Schoenfeld residuals. Kaplan–Meier survival curves were used to illustrate the association between serum TSH levels and all-cause mortality, with differences tested by a log rank test. Hazard ratios (HR) were calculated with a 95% confidence interval (CI). A value of $P < 0.05$ was considered statistically significant. This manuscript was written in accordance with the STROBE statement, giving guidelines for reporting results from observational studies (29). All statistical analyses were performed using SAS 9.1 (SAS Institute, Inc., Cary, NC, USA).

Results

Table 1 shows the baseline characteristics of individuals with and without decreased serum TSH levels. Of the 3651 individuals available for this analysis, 270 had decreased serum TSH levels (7.4%). Compared to euthyroid subjects, individuals with decreased serum TSH levels were older, and less often current smokers, but more often former smokers. Furthermore, participants with decreased serum TSH levels were more often hypertensive and overweight, reported more often a history of stroke, and had higher fibrinogen levels.

During follow-up, 299 individuals (6.9%) died corresponding to 9.92 deaths per 1000 person years. More individuals with decreased serum TSH levels (15.98 deaths per 1000 person years) deceased than individuals with serum TSH levels within the reference range (9.45 deaths per 1000 person years; relative risk: 1.67; 95% CI: 1.19, 2.33). Also, survival time was shorter in subjects with decreased serum TSH levels compared to euthyroid individuals (log rank test; $P = 0.003$). Proportional hazard assumption was met by all models.

Table 1 Baseline characteristics of individuals stratified by serum TSH levels. Data are given as numbers (percent) or median (25 and 75th percentile).

	Serum TSH levels ≥ 0.25 mIU/l ($n = 3381$)	Serum TSH levels < 0.25 mIU/l ($n = 270$)	P^a
Sex (males)	1807 (52.4%)	155 (57.4%)	0.111
Age (years)	48.0 (35.0; 62.0)	61.0 (48.0; 69.0)	<0.001
Smoking status ^b			
Former smokers	1138 (33.7%)	111 (41.1%)	0.041
Current smokers	947 (28.0%)	64 (23.7%)	
Hypertension	1724 (51.0%)	161 (59.6%)	0.006
Stroke	67 (2.0%)	15 (5.6%)	<0.001
Myocardial infarction	109 (3.2%)	12 (4.4%)	0.281
Diabetes mellitus type 2	249 (7.4%)	26 (9.6%)	0.175
Body mass index (kg/m ²)	26.7 (23.6; 29.9)	27.4 (24.9; 30.0)	0.029
Cholesterol (mmol/l)	5.7 (4.9; 6.5)	5.6 (4.9; 6.3)	0.231
Fibrinogen (mmol/l)	8.3 (7.3; 9.9)	9.3 (7.9; 10.9)	<0.001
Time of blood collection (before 1200 h)	2038 (60.3%)	168 (62.2%)	0.530

Table refers to subjects without increased serum TSH levels > 2.12 mIU/l.

^a χ^2 -test (qualitative data) and Wilcoxon test (quantitative data).

^bReference lifetime nonsmokers.

Table 2 displays the association between decreased serum TSH levels and all-cause mortality. The crude model revealed a significant association between decreased serum TSH levels and all-cause mortality. This association was no longer present after adjustment for age and sex. Figure 1 shows the cumulative hazard functions for all-cause mortality by serum TSH levels adjusted for age and sex. Further adjustments for smoking habits, hypertension, stroke, myocardial infarction, diabetes mellitus type 2, BMI, cholesterol, and fibrinogen had only small effects on the results (Table 2). There were also no statistically significant independent associations between decreased serum TSH levels and all-cause mortality when increasing the TSH cutoff to 0.3 mIU/l (7, 9) or 0.4 mIU/l (15, 18) (Table 2). Furthermore, no association between TSH in the reference range (the group below the first quintile was defined as reference group) and mortality was detected (Table 2). Interactions of decreased serum TSH levels with hypertension, myocardial infarction, stroke, serum cholesterol levels, and BMI were sequentially added to model 3. None of these interactions attained statistical significance. Sex-stratified analyses showed no significant association between decreased serum TSH levels and mortality (men: HR, 1.00; 95% CI, 0.66, 1.51; $P = 0.997$; women: HR, 0.72; 95% CI, 0.34, 1.51; $P = 0.384$) in the full-adjusted models. Also, analyses stratified by the time of blood collection (before and after 1200 h) revealed no change of results.

Table 2 Association of decreased serum TSH levels and TSH levels in the reference range with all-cause mortality.

Exposition ^a	Number of deaths in the exposure group	Model 1	Model 2	Model 3
		HR (95% CI)	HR (95% CI)	HR (95% CI)
TSH < 0.25 mIU/l (<i>n</i> = 270)	35	1.69 (1.19; 2.40) [†]	0.95 (0.67; 1.36)	0.93 (0.65; 1.33)
TSH < 0.3 mIU/l (<i>n</i> = 396)	49	1.63 (1.20; 2.21) [†]	0.92 (0.67; 1.25)	0.93 (0.68; 1.27)
TSH < 0.4 mIU/l (<i>n</i> = 727)	81	1.50 (1.17; 1.94) [†]	0.91 (0.71; 1.18)	0.93 (0.72; 1.20)
TSH ≤ 0.03 mIU/l (<i>n</i> = 15)	2	0.94 (0.23; 3.79)	0.97 (0.24; 3.90)	1.06 (0.26; 4.30)
0.03 mIU/l < TSH < 0.25 mIU/l (<i>n</i> = 255)	33	1.76 (1.23; 2.51) [†]	0.96 (0.67; 1.38)	0.93 (0.65; 1.34)
TSH in the reference range				
0.45 mIU/l < TSH ≤ 0.61 mIU/l (<i>n</i> = 673)	52	0.72 (0.51; 1.03)	0.93 (0.65; 1.32)	0.91 (0.64; 1.30)
0.61 mIU/l < TSH ≤ 0.78 mIU/l (<i>n</i> = 662)	49	0.69 (0.48; 0.99)*	0.99 (0.69; 1.42)	0.93 (0.65; 1.33)
0.78 mIU/l < TSH ≤ 1.05 mIU/l (<i>n</i> = 681)	44	0.60 (0.42; 0.88) [†]	1.06 (0.73; 1.54)	1.09 (0.75; 1.58)
1.05 mIU/l < TSH (<i>n</i> = 666)	45	0.64 (0.44; 0.93)*	1.26 (0.87; 1.82)	1.21 (0.83; 1.76)

**P* < 0.05, [†]*P* < 0.01. HR, hazard ratio; CI, 95% confidence interval; model 1, unadjusted Cox regression; model 2, Cox regression adjusted for age and sex; model 3, Cox regression adjusted for age, sex, smoking status, hypertension, stroke, myocardial infarction, diabetes mellitus type 2, body mass index, cholesterol, and fibrinogen.

^aReference group: euthyroid individuals above the respective cutoff; for analysis regarding the TSH reference range (0.25 mIU/l; 2.12 mIU/l), individuals < 0.45 mIU/l (first quintile of TSH in the reference range) are in the reference group.

Of the 299 deceased individuals, the cause of death was not available from 41 individuals. Of the remaining 258 decedents, 96 individuals (25 women; 32.1%) died from cancer (ICD code: C00–C97) and 97 individuals (29 women; 32.4%) from cardiovascular diseases (ICD code: I10–I97). After adjustment for confounders, Cox regression revealed no significant associations of decreased serum TSH levels with cancer (HR, 1.05; 95% CI, 0.57, 1.93; *P* = 0.890) and cardiovascular mortality (HR, 1.08; 95% CI, 0.61, 1.91; *P* = 0.803). When alternating the TSH cutoff to 0.3 mIU/l, Cox regression models disclosed a HR of 1.05 (95% CI, 0.67, 1.63; *P* = 0.846) for cancer and 0.82 (95% CI, 0.52, 1.30; *P* = 0.394) for cardiovascular mortality.

Figure 1 Cumulative hazard functions for participants with and without decreased TSH.

Finally, we divided subjects with serum TSH levels below 0.25 mIU/l into those with subclinical (243 subjects; 103 women) and those with overt hyperthyroidism (27 subjects; 15 women). When applying Cox regression models, there was no association of subclinical or overt hyperthyroidism with all-cause, cancer, and cardiovascular mortality (Table 3).

Discussion

In the present study, we analyzed associations of decreased serum TSH levels with all-cause, cancer, and cardiovascular mortality. We detected no such associations. Applying an alternative cutoff for decreased serum TSH levels as well as dividing individuals with decreased serum TSH levels into those with subclinical and overt hyperthyroidism did not change these results materially.

With respect to decreased serum TSH levels, our results are in line with two studies (12, 16). Two other studies (7, 11) reported an association between decreased serum TSH levels and all-cause mortality. Contrary to one study (11), we detected no relationship between overt hyperthyroidism and all-cause mortality. Focussing on subclinical hyperthyroidism, our results are in concordance with most of the previous studies (3, 9, 15, 18) and meta-analyses (10, 14). However, one study (13) and one meta-analysis (8) did not confirm this finding. Haentjens *et al.* (8) concluded that the increased likelihood of death is not immediate after the diagnosis of subclinical hyperthyroidism, but became apparent after the second year and continued up to 10 years after the diagnosis of subclinical hyperthyroidism. Haentjens *et al.* (8) included seven studies (3, 7, 9, 12, 13, 18, 30) in their meta-analysis. Two of those (7, 12) did not explicitly focus on the association of subclinical hyperthyroidism with all-cause mortality, e.g. Parle *et al.* (12) compared participants with serum TSH levels

Table 3 Association of subclinical and overt hyperthyroidism with all-cause, cancer, and cardiovascular mortality.

	Model 1		Model 2		Model 3	
	Subclinical hyperthyroidism (n=243; 31 deaths)	Overt hyperthyroidism (n=27; 4 deaths)	Subclinical hyperthyroidism (n=243; 31 deaths)	Overt hyperthyroidism (n=27; 4 deaths)	Subclinical hyperthyroidism (n=243; 31 deaths)	Overt hyperthyroidism (n=27; 4 deaths)
	HR (95% CI)		HR (95% CI)		HR (95% CI)	
All-cause mortality	1.66 (1.14; 2.41)*	1.98 (0.74; 5.31)	0.94 (0.65; 1.37)	1.01 (0.38; 2.70)	0.91 (0.63; 1.33)	1.08 (0.40; 2.96)
Cancer mortality	1.91 (1.02; 3.57)*	1.61 (0.22; 11.57)	1.07 (0.57; 2.00)	0.81 (0.11; 5.85)	1.05 (0.56; 1.99)	1.07 (0.15; 7.82)
Cardiovascular mortality	1.92 (1.03; 3.61)*	4.57 (1.44; 14.44)*	0.95 (0.50; 1.78)	2.02 (0.64; 6.40)	0.97 (0.51; 1.83)	2.07 (0.63; 6.87)

* $P < 0.05$. HR, hazard ratio; CI, confidence interval; model 1, unadjusted Cox regression; model 2, Cox regression adjusted for age and sex; model 3, Cox regression adjusted for age, sex, smoking status, hypertension, stroke, myocardial infarction, diabetes mellitus type 2, body mass index, cholesterol, and fibrinogen.

of ≤ 0.5 mIU/l with those > 0.5 mIU/l. Contrary to the meta-analysis by Ochs *et al.* (10), Haentjens *et al.* (8) considered the study by Parle *et al.* (12) as one which has detected a significant association between subclinical hyperthyroidism and mortality. The reason for this is that Parle *et al.* (12) reported estimators for five different follow-up times. For a follow-up time of 10 years, they detected no association but for follow-up times of 2, 3, 4, and 5 years. This might be one explanation for conflicting results between these meta-analyses (8, 10). Also, the selection of studies included might be responsible for conflicting results between these meta-analyses. Völzke *et al.* (17) included two studies into their meta-analyses, Singh *et al.* (14) included three studies, and Ochs *et al.* (10) included five studies. Furthermore, the meta-analysis by Haentjens *et al.* was the first which included studies of patients with co-morbidities (9, 13, 30).

Furthermore, four (7, 12, 13, 30) of the seven studies included in the meta-analysis by Haentjens did not adjust their models for major confounders such as age and smoking. Particularly, smoking is an important risk factor in the pathogenesis of thyroid diseases (31, 32). Because smoking is also an important predictor of mortality (33), the impact of hyperthyroidism on mortality might be overestimated when smoking is not considered (17). In our analysis, a statistically significant association between decreased serum TSH levels and mortality was no longer present even after adjustment for age. Since different studies did not adjust for the same covariables, it should be decided carefully which studies to include into a meta-analysis. Conclusions from meta-analyses may be hampered, if they include original results from multivariable analyses adjusted for different sets of covariables. In our study, confounders apart from age and sex did not change the results materially, but in other populations, these confounders might play a more important role.

Apart from different nonconsideration of major confounders, there are three further factors that might be responsible for contradictory results. Firstly, different definitions of hyperthyroidism might have led

to conflicting results. Usually, the cutoff for serum TSH levels varied between 0.3 (7) and 0.5 mIU/l (12). Most of these studies considered FT₄ levels (3, 9, 11, 13, 15, 16, 18), whether others did not (7, 12). Secondly, differences in follow-up time play a crucial role. In previous studies on the association between hyperthyroidism and mortality, the mean follow-up time varied between 3.7 (7) and 20 years (18). Short follow-up times in smaller studies might be problematic, since the impact of the disease on mortality might be too weak. Otherwise, analysis based on long follow-up times might underestimate the influence of the exposure on mortality for misclassification bias due to change in exposure over time. In the present study, participants were informed about their laboratory results. The awareness of thyroid diseases might have led to frequent medical monitoring and early treatment decisions, which also might have introduced bias due to change in the exposure variable. This might have resulted in an underestimation of the effect of hyperthyroidism on mortality in the present study, particularly for overt hyperthyroidism. Finally, different age structures of the selected populations might have given rise to discrepant results. Some of previous studies on the association of hyperthyroidism with mortality focused on participants older than 60 years (3, 7, 12, 13, 15).

With respect to cardiovascular mortality, results from our study are in concordance with most of the previously reported studies (3, 11, 12, 18) and meta-analyses (10, 14, 17). Two other studies (7, 9) detected an association between decreased serum TSH levels and cardiovascular mortality. Although Iervasi *et al.* (9) detected no association between mild hyperthyroidism with all-cause mortality, they demonstrated that mild hyperthyroidism is an independent risk factor for cardiovascular mortality in their study. Results from this study (9) are not comparable to those from our study because they investigated this association in a subgroup of cardiac patients. While the association between decreased serum TSH levels and cardiovascular mortality is conflicting, the association between decreased serum TSH levels and nonfatal events

including atrial fibrillation (3), high plasma fibrinogen levels (4), and left ventricular hypertrophy (6) is well established. Parts of this discrepancy might be explained by the fact that atrial fibrillation *per se* is at least not tightly related to increased mortality (34). Furthermore, one might assume that patients having subclinical hyperthyroidism diagnosed at the time of a cardiovascular event might be treated for the thyroid disorder or referred to a more intense clinical follow-up.

In concordance with two studies (19, 23), we detected no association between hyperthyroidism and cancer mortality, while three studies (20–22, 24) demonstrated such an association. However, these studies did not use population-based samples (19–24), but were conducted in patient cohorts undergoing radioiodine treatment. It is the objective of current research to answer the question whether increased mortality in these patients might be related to the exposure of ionizing radiation. Selection bias might represent an alternative explanation for the increased mortality in radioiodine patients. At least in some regions only, those patients undergo radioiodine treatments that have contraindications against surgery, i.e. elder patients with co-morbidities. Thus, increased mortality in these patients might be related to age and poor general condition rather than to thyroid dysfunction or radioiodine application.

The size of the study population represents a major limitation of the present study. Although in the present study risk estimators were mostly close to 1, a weak association between decreased serum TSH levels and all-cause mortality with an HR of <1.65 might have been missed from detection due to power reasons. In particular, the number of subjects who were classified as overt hyperthyroid and those who died from cancer and cardiovascular diseases was too low. Therefore, further research is strongly needed in that respect. Another limitation of our study is the less well-standardized time of blood specimen collection. It has been previously reported that serum TSH levels might alter by daytime (35). Therefore, we performed analyses stratified by the time of blood sampling, which did not change the results materially. Strengths of our study include the population-based approach and the definition of thyroid dysfunction using not only TSH but also free thyroid hormones.

In conclusion, we detected no independent association of decreased serum TSH levels with all-cause, cancer, and cardiovascular mortality in the adult northeast population of Germany. Although our study has some strengths, we cannot finally conclude on therapeutical implication to treat or not to treat individuals with subclinical thyroid diseases.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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