Thyroid Status, Disability and Cognitive Function, and Survival in Old Age

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Context Despite the equivocal outcomes of randomized controlled trials, general clinical opinion favors screening and treatment of elderly individuals with subclinical thyroid disorders.

Objectives To determine whether subclinical thyroid dysfunction should be treated in old age and the long-term impact of thyroid dysfunction on performance and survival in old age.

Design, Setting, and Participants A prospective, observational, population-based follow-up study within the Leiden 85-Plus Study of 87% of a 2-year birth cohort (1912-1914) in the municipality of Leiden, the Netherlands. A total of 599 participants were followed up from age 85 years through age 89 years (mean [SD] follow-up, 3.7 [1.4] years).

Main Outcome Measures Complete thyroid status at baseline; disability in daily life, depressive symptoms, cognitive function, and mortality from age 85 years through 89 years.

Results Plasma levels of thyrotropin and free thyroxine were not associated with disability in daily life, depressive symptoms, and cognitive impairment at baseline or during follow-up. Increasing levels of thyrotropin were associated with a lower mortality rate that remained after adjustments were made for baseline disability and health status. The hazard ratio (HR) for mortality per SD increase of 2.71 mIU/L of thyrotropin was 0.77 (95% confidence interval [CI], 0.63-0.94; $P=.009$). The HR for mortality per SD increase of 0.21 ng/dL (2.67 pmol/L) of free thyroxine increased 1.16-fold (95% CI, 1.04-1.30; $P=.009$).

Conclusions In the general population of the oldest old, elderly individuals with abnormally high levels of thyrotropin do not experience adverse effects and may have a prolonged life span. However, evidence for not treating elderly individuals can only come from a well-designed, randomized placebo-controlled clinical trial.

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THYROID DYSFUNCTION IN ELderly individuals often occurs unnoticed. Hence, screening for both hypothyroidism and hyperthyroidism has been recommended, especially in old age.[1,2] Apart from finding individuals with previously unrecognized overt hypothyroidism and hyperthyroidism, screening will also reveal persons with subclinical thyroid dysfunction. These individuals have abnormal plasma levels of thyrotropin combined with normal plasma levels of free thyroxine.

Subclinical thyroid dysfunction has been associated with various negative clinical outcomes and an increased risk of overt thyroid dysfunction. Two recent literature reviews of subclinical thyroid dysfunction rated the evidence as inconclusive for an association between subclinical thyroid disease and clinical symptoms.[3,4] Furthermore, the outcomes of randomized placebo-controlled clinical trials evaluating the treatment effect of subclinical thyroid disease on symptoms and lipid levels are inconsistent.[5-11] Despite these ambiguities, policy makers have recommended screening and treatment of subclinical thyroid dysfunction to prevent progression to overt thyroid dysfunction and to improve clinical outcomes, especially in elderly individuals.[12-15]

See also pp 2600, 2632, and 2651.

To determine whether subclinical thyroid dysfunction should be treated in old age, clinical correlates of thyroid status were studied in an unselected population-based cohort of 599 elderly individuals aged 85 years. Moreover, these elderly individuals were prospectively followed up to determine the long-term impact of thyroid dysfunction on performance and survival in old age.

METHODS

Participants

The Leiden 85-Plus Study is a prospective, population-based study of all individuals aged 85 years (birth cohort, 1912-1914) and living in Leiden, the Netherlands between September 1997 and September 1999. There were no exclusion criteria. Of the 705 eligible individuals, 14 died before they could be enrolled and 92 refused to participate, resulting in a cohort of 599 partici-

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pants enrolled at baseline (response rate of 87%).[16] Baseline plasma samples were obtained from 558 participants. Starting within 1 month after their 85th birthday, participants received annual home visits during which extensive data on health, functioning, and well-being were collected. The ethical committee of the Leiden University Medical Center approved the study and all participants provided oral informed consent for study participation. Further information on the design of the study and characteristics of the cohort have been published elsewhere.[17]

Thyroid Status

Samples were stored at –80°C. Plasma levels of thyrotropin and free thyroxine were measured in 1 batch with an Elecsys 2010 system (Hitachi, Tokyo, Japan) in a completely automated laboratory robot. An electrochemiluminescence technique was applied (Boehringer, Mannheim, Germany). The plasma level of free triiodothyronine was measured by a microparticle enzyme immunoassay (Abbott Diagnostics, Abbott Park, Ill). For thyrotropin, the variation coefficients were between 5% and 11%; free thyroxine, between 5% and 8%; and free triiodothyronine, between 3% and 8%. In our laboratory, the reference values for thyrotropin were 0.3 mIU/L to 4.8 mIU/L; free thyroxine, 1.01 to 1.79 ng/dL (13-23 pmol/L); and free triiodothyronine, 305 to 532 pg/dL (4.7-8.2 pmol/L). The ratio of free triiodothyronine to free thyroxine was considered to be a marker of the 5′deiodination activity.

Information on the use of thyroid medication (antithyroid medication and/or L-thyroxine) was obtained annually from computerized registries of pharmacy records, which were virtually complete for all participants from age 85 years through 87 years. All participants with newly detected overt thyroid dysfunction during the baseline assessment were advised to consult with their primary care physician for further evaluation and to consider treatment. To study the clinical course of subclinical thyroid disorders, assessments of thyrotropin and free thyroxine were repeated at age 88 years.

Performance

Performance was annually assessed using the Groningen Activity Restriction Scale, which assesses disability in 9 activities of daily living (ADLs) and 9 instrumental ADLs.[18] Disability scores in ADLs and in instrumental ADLs ranges from 9 points (fully independent in all activities) to 36 points (fully dependent in all activities).

Depressive symptoms were annually assessed with the 15-item Geriatric Depression Scale (GDS-15), a screening instrument used in elderly individuals. The GDS-15 could only be administered to those with a Mini-Mental State Examination (MMSE) score of higher than 18 points. Scores on the GDS-15 range from zero points (no depressive symptoms) to 15 points. Participants with a GDS-15 score of 4 points or more were considered depressed.[19]

Global cognitive function was assessed annually with the MMSE. The MMSE scores range from zero points (very severe cognitive impairment) to 30 points (optimal cognitive function). In participants with MMSE scores above 18 points, various domains of cognitive function were further investigated by the Stroop test, the Letter Digit Coding test, and the Word Learning Test.[20,21] The Stroop test assesses attention; the outcome parameter used was the total number of seconds to complete the third Stroop card containing 40 words. The Letter Digit Coding test assesses cognitive speed; the outcome parameter used was the total number of correct digits filled in within 60 seconds. The 12-word learning test assesses immediate and delayed memory. The outcome parameter of immediate recall was the sum of recalled pictures in 3 procedures (range, 0-36 pictures). After 20 minutes, delayed recall was tested; the outcome parameter used was the number of pictures recalled (range, 0-12 pictures).

Survival

All participants were followed up prospectively for mortality until age 89 years (censoring date). The date of death was obtained from the civic registry of Leiden. Survival time was defined as number of days between the 85th birthday and the censoring date, or the date of death. Shortly after the civic registry reported the death of a participant, the treating physician (primary care physician or nursing home physician) was interviewed to obtain the cause of death using a standardized questionnaire. Two senior internal medicine specialists, who were unaware of the present analyses, determined the causes of death by consensus according to the 10th version of the *International Classification of Diseases (ICD-10)*. Causes of death were divided into 2 groups: cardiovascular mortality (*ICD-10* codes I00-I99, I20-I25, and I60-I69) and noncardiovascular mortality (all other *ICD-10* codes).

Possible Confounders

Self-reported educational level was dichotomized around 6 years of schooling and entered as a dichotomous variable in the analyses. Indication of baseline health status was obtained by using plasma levels of albumin and C-reactive protein, number of chronic diseases, MMSE score at baseline, and subjective health on a 5-point scale. Based on medical history, blood analysis, or electrocardiogram at baseline, the included chronic diseases were history of type 2 diabetes, myocardial infarction, stroke, chronic obstructive pulmonary disease, arthritis, and Parkinson disease.

Statistical Analysis

Thyroid function was investigated using 2 different strategies. First, based on plasma levels of thyrotropin and free thyroxine, thyroid status was stratified according to general clinical consensus.[3] Plasma levels of thyrotropin between 0.3 mIU/L to 4.8 mIU/L were defined as normal, plasma thyrotropin levels above 4.8 mIU/L were defined as abnormally high, and plasma thyrotropin levels below 0.3 mIU/L were defined as abnormally low. *Overt hypothyroidism* was defined as having an abnormally high thyrotropin level combined with a free thyroxine level be-

low 1.01 ng/dL (13 pmol/L). *Subclinical hypothyroidism* was defined as an abnormally high thyrotropin level combined with a normal level of free thyroxine (1.01-1.79 ng/dL [13-23 pmol/L]). *Overt hyperthyroidism* was defined as an abnormally low thyrotropin level combined with a free thyroxine level above 1.79 ng/dL (23 pmol/L). *Subclinical hyperthyroidism* was defined as an abnormally low level of thyrotropin combined with a normal free thyroxine level (1.01-1.79 ng/dL [13-23 pmol/L]). In the second strategy, levels of thyroid hormones were entered in the analytic models as continuous variables. The results of these analyses are presented per SD increase for each of the hormones.

To investigate the feedback between free thyroxine and thyrotropin, the association between the logarithms was assessed using linear regression. The association between levels of thyroid hormones at baseline and performance during follow up was analyzed with linear mixed models.[22,23] These models included the terms *level of thyroid hormone*, *time*, and *interaction of level of thyroid hormone and time*. The estimate for thyroid hormone level reflects the cross-sectional association between thyroid hormone and performance, and is presented as the baseline difference. The estimate for time reflects the annual change in performance, and is presented as change over time. The estimate for interaction of level of thyroid hormone and time reflects the additional annual change in performance per SD increase of thyroid hormones at baseline and is presented as additional annual change. All estimates were adjusted for sex and educational level. We standardized the estimates per SD increase of thyroid hormone levels by using the formula: (individual plasma level – mean plasma level in the population)/SD in the population.

A Kaplan-Meier curve illustrates the association between the clinical strata of thyroid function and all-cause mortality. Differences in survival between these groups were compared with Cox regression. Crude hazard ratios (HRs) are expressed per SD increase of thyroid hormones at baseline and after adjustment for sex. Assumption for proportionality of the mortality hazards was assessed by visual inspection of cumulative hazard logarithm plots. To exclude confounding by baseline differences, we further adjusted the crude HRs for differences in baseline disability and health status (including plasma levels of albumin and C-reactive protein, number of chronic diseases, MMSE score at baseline, and subjective health as indicated above). None of these variables were entered as time-dependent covariates. Finally, we repeated the analyses and included only participants with normal thyroid function.

The comparisons between the subgroups of clinical thyroid status and the analyses with the thyroid function as continuous variables were all preplanned. We also performed several post hoc analyses (eg, the analyses in participants with normal thyroid function). We used SPSS software (version 12.0.1, SPSS Inc, Chicago, Ill) for all statistical analyses.

RESULTS

At baseline, we obtained complete thyroid status for 558 participants. Baseline characteristics of these participants, all aged 85 years, are presented in TABLE 1. FIGURE 1 presents the number of elderly individuals participating at each year of follow up. In total, 70 participants refused further participation (≤5% per year). Twelve died within 1 month after refusal and another 35 died at or by age 89 years. During follow-up, 209 (37%) of 558 participants died. The mortality rate increased from 27% in those without chronic diseases at baseline to 36% in those with 1 chronic disease and to 51% in participants who had 2 or more chronic diseases.

Thyroid Status

Of the 558 participants, 472 (85%) had normal thyroid function, 67 (12%) had

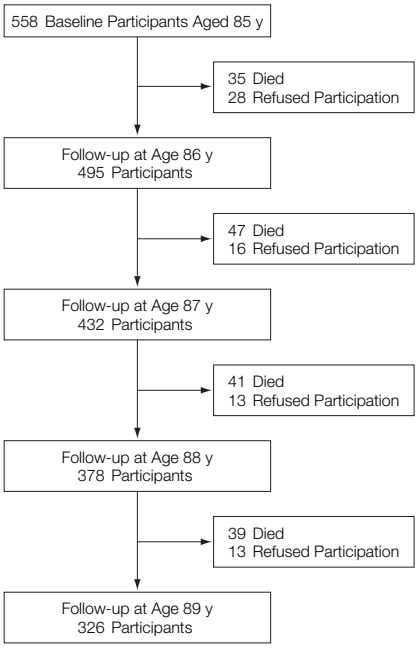
Table 1. Baseline Characteristics of Participants Aged 85 Years

	No. (%) of Participants (N = 558)
Demographics	
Women	369 (66)
Schooling >6 y	193 (35)
Independent living	455 (82)
Performance	
Independent in ADLs	458 (82)
Independent in instrumental ADLs	218 (39)
Good cognitive function (MMSE ≥24)	386 (69)
Severe cognitive impairment (MMSE <19)	91 (16)
No severe depressive symptoms (GDS-15 <4)*	358 (77)
Clinical thyroid status	
Abnormally low thyrotropin	
Overt hyperthyroidism	2 (0.4)
Subclinical hyperthyroidism	17 (3)
Normal thyrotropin	
Euthyroidism	472 (85)
Abnormally high thyrotropin	
Subclinical hypothyroidism	30 (5)
Thyrotropin level of 4.80 to 10 mIU/L	25 (4)
Thyrotropin level ≥10 mIU/L	5 (<1)
Overt hypothyroidism†	37 (7)
Thyroid medication	21 (4)
Antithyroid medication and L-thyroxine	4 (<1)
L-thyroxine	17 (3)

Abbreviations: ADLs, activities of daily living; GDS-15, Geriatric Depression Scale 15 items; MMSE, Mini-Mental State Examination.
*Only administered in 436 participants with an MMSE score of 18 points or higher.
†Thyrotropin range, 4.86 mIU/L to 33.0 mIU/L.

abnormally high levels of thyrotropin, and 19 (3%) had abnormally low levels of thyrotropin (Table 1). At baseline, 21 participants (4%) were taking thyroid medication (L-thyroxine and/or antithyroid medication). Thirty-nine participants with newly detected overt thyroid dysfunction were referred to their primary care physician or nursing home physician for further clinical evaluation. Pharmacy records were checked for these 39 participants at age 86 years and at age 87 years—none were taking L-thyroxine and/or antithyroid medication. Apparently, among this age group the primary care physicians do not start treatment for disorders that are identified by screening only.

Figure 1. Flow of Participants



There was a significant, inverse correlation at baseline between plasma levels of thyrotropin and free thyroxine (r=–0.38, P<.001). TABLE 2 presents several baseline characteristics for clinical strata of thyroid function. Higher levels of thyrotropin were associated with a higher body mass index (P=.02), higher cholesterol levels (P=.04), and higher levels of triglycerides (P=.004). Levels of C-reactive protein were not associated with thyroid function.

To study the course of thyroid status over time, assessments of thyrotropin and free thyroxine were repeated at age 88 years in 376 participants. A total of 296 (95%) of 310 participants had normal thyroid function at ages 85 and 88 years. Twenty-one of the 30 participants with subclinical hypothyroidism at baseline were reassessed at age 88 years. None had developed overt hypothyroidism, 8 continued to have subclinical hypothyroidism, 11 had normal thyroid function, and 2 participants had overt hyperthyroidism at age 88 years. Thyroid status of 12 of the 17 participants with subclinical hyperthyroidism at baseline was reassessed at age 88 years. One participant had developed overt hyperthyroidism, 5 participants had subclinical hyperthyroidism, 5 participants now had normal thyroid function, and 1 participant developed subclinical hypothyroidism.

Performance

At baseline, there was no association between levels of thyrotropin and disability in ADLs, disability in instrumental ADLs, depressive symptoms, and cognitive function (TABLE 3, baseline differences per SD, all P>.30). All measures of performance significantly deteriorated over time (Table 3, change over time, all P<.001). Increasing baseline levels of thyrotropin were not associated with an accelerated increase in disability in ADLs, depressive symptoms, or cognitive decline during follow-up (Table 3, additional annual change per SD, all P>.20). However, increasing thyrotropin levels at baseline were associated with a significant decelerated increase in disability in instrumental ADLs (–0.12 per year per SD thyrotropin at baseline, P=.03), the interpretation being that higher plasma levels of thyrotropin at baseline protected against dependency in instrumental ADLs during follow-up.

At baseline, there was also no association between levels of free thyroxine and disability in ADLs, disability in instrumental ADLs, depressive symptoms, and cognitive function (Table 3, baseline differences per SD, all P>.10). All measures of performance significantly deteriorated over time (Table 3, change over time, all P<.001). Increasing levels of free thyroxine at baseline were not associated with an accelerated increase in disability in ADLs, disability in instrumental ADLs, and depressive symptoms over time, neither with an accelerated cognitive decline

Table 2. Baseline Characteristics for Clinical Strata of Thyroid Function*

	Abnormally Low Thyrotropin†			Abnormally High Thyrotropin§		
	Overt Hyperthyroidism	Subclinical Hyperthroidism	Normal Level of Thyrotropin‡	Subclinical Hypothyroidism	Overt Hypothyroidism	*P* Value for Trend‖
No. of participants	2	17	472	30	37	
Body mass index	21.5 (2.3)	25.6 (5.1)	27.1 (4.5)	27.7 (3.8)	28.3 (4.8)	.02
Total cholesterol, mmol/L	5.6 (0.7)	5.4 (1.5)	5.7 (1.1)	6.4 (1.3)	5.8 (1.0)	.04
Triglycerides, mmol/L	1.3 (0.5)	1.7 (1.1)	1.5 (0.7)	1.9 (1.1)	1.9 (1.2)	.004
C-reactive protein, mg/L	4.8 (2.0)	5.4 (2.6)	4.8 (2.9)	7.4 (2.6)	4.4 (7.9)	.77

SI conversion factors: To convert total cholesterol, divide by 0.0259; triglycerides, divide by 0.0113.
*Data are presented as mean (SD) except for C-reactive protein, which is geometric mean (SD).
†Defined as below 0.3 mIU/L.
‡Defined as 0.3 to 4.8 mIU/L.
§Defined as above 4.8 mIU/L.
‖Differences in mean baseline characteristics were analyzed with analysis of variance test for linearity.

(Table 3, additional annual change per SD, all $P>.08$).

Survival

During follow-up until age 89 years, 209 (37%) of 558 participants died. FIGURE 2 presents the cumulative all-cause mortality based on the clinical stratification of thyroid function. Thyroid function was significantly associated with mortality; participants with abnormally low levels of thyrotropin at baseline had highest mortality rate, and participants with abnormally high thyrotropin levels and abnormally low levels of free thyroxine had the lowest mortality rate (Cox regression, P for trend=.03).

The sex-adjusted HRs for all-cause mortality per SD increase in baseline level of thyrotropin and free thyroxine appear in TABLE 4. Increasing levels of thyrotropin were associated with decreased mortality. Mortality per SD increase of thyrotropin at baseline of 2.71 mIU/L was 0.76-fold lower (95% confidence interval [CI], 0.62-0.92; $P=.005$). This decreased mortality risk remained unchanged after adjustment for baseline disability and health status (including plasma levels of albumin and C-reactive protein, number of chronic diseases, MMSE score at baseline, and subjective health). Moreover, increasing levels of free thyroxine were associated with increased all-cause mortality. Mortality risk per SD increase of baseline free thyroxine of 0.21 ng/dL (2.67 pmol/L) was 1.22-fold higher (95% CI, 1.08-1.37, $P=.001$). After adjustment for baseline disability and health status, the increased mortality risk remained. The increased mortality risk also remained in a restricted analysis that included par-

Table 3. Performance of Participants Aged 85 Years Depending on Baseline Levels of Thyrotropin, Free Thyroxine, and Free Triiodothyronine (N=558)*

	Baseline Difference per SD†		Change Over Time		Additional Annual Change per SD	
	Estimate (SE)	*P* Value	Estimate (SE)	*P* Value	Estimate (SE)	*P* Value
Thyrotropin‡						
Disability, points						
ADLs	−0.05 (0.28)	.86	1.2 (0.06)	<.001	−0.01 (0.05)	.87
Instrumental ADLs	0.06 (0.34)	.87	2.5 (0.06)	<.001	−0.12 (0.06)	.03
Depressive symptoms, points	−0.06 (0.13)	.64	0.29 (0.03)	<.001	0.02 (0.03)	.53
Global cognitive function, points	−0.03 (0.26)	.93	−0.79 (0.04)	<.001	0.01 (0.04)	.96
Attention, s	1.3 (1.4)	.35	1.4 (0.37)	<.001	−0.47 (0.39)	.23
Processing speed, digits	−0.22 (0.32)	.49	−0.64 (0.05)	<.001	−0.01 (0.06)	.90
Immediate memory, pictures	−0.18 (0.30)	.55	−1.0 (0.06)	<.001	0.07 (0.06)	.26
Delayed memory, pictures	−0.10 (0.14)	.46	−0.48 (0.03)	<.001	0.03 (0.03)	.38
Free Thyroxine§						
Disability, points						
ADLs	0.41 (0.29)	.15	1.2 (0.06)	<.001	0.11 (0.06)	.67
Instrumental ADLs	0.55 (0.34)	.11	2.5 (0.06)	<.001	0.10 (0.07)	.09
Depressive symptoms, points	0.06 (0.12)	.62	0.28 (0.03)	<.001	−0.01 (0.03)	.95
Global cognitive function, points	−0.02 (0.27)	.94	−0.78 (0.04)	<.001	−0.06 (0.04)	.18
Attention, s	1.7 (1.3)	.20	1.4 (0.37)	<.001	0.32 (0.40)	.42
Processing speed, digits	−0.23 (0.30)	.44	−0.64 (0.06)	<.001	−0.07 (0.06)	.22
Immediate memory, pictures	−0.27 (0.28)	.34	−1.0 (0.06)	<.001	−0.10 (0.07)	.14
Delayed memory, pictures	−0.13 (0.13)	.32	−0.48 (0.03)	<.001	−0.06 (0.03)	.08
Free Triiodothyronine‖						
Disability, points						
ADLs	−1.7 (0.28)	<.01	1.2 (0.06)	<.001	−0.21 (0.06)	<.001
Instumental ADLs	−2.3 (0.33)	<.001	2.5 (0.06)	<.001	−0.04 (0.58)	.58
Depressive symptoms, points	−0.29 (0.12)	.02	0.31 (0.03)	<.001	−0.07 (0.04)	.04
Global cognitive function, points	1.3 (0.26)	<.001	−0.80 (0.04)	<.001	0.11 (0.042)	.008
Attention, s	−0.34 (1.3)	.80	1.4 (0.36)	<.001	0.42 (0.40)	.30
Processing speed, digits	1.2 (0.30)	<.001	−0.67 (0.06)	<.001	0.10 (0.06)	.10
Immediate memory, pictures	0.80 (0.28)	.005	−1.0 (0.63)	<.001	0.003 (0.07)	.97
Delayed memory, pictures	0.41 (0.13)	.003	−0.49 (0.03)	<.001	0.01 (0.01)	.89

Abbreviation: ADLs, activities of daily living.
*All estimates by linear mixed models, adjusted for sex and educational level. Depressive symptoms, attention, processing speed, immediate recall and delayed recall were not administered in participants with Mini-Mental State Examination scores below 19 points.
†Baseline difference per SD is the estimate for the level of thyroid hormone and reflects the cross-sectional association between thyroid hormone and performance.
‡The mean (SD) level is 2.54 (2.71) mIU/L.
§The mean (SD) level is 1.13 (0.21) ng/dL [14.55 {2.67} pmol/L].
‖The mean (SD) level is 220 (3.57) pg/dL [3.39 {0.55} pmol/L].

ticipants with normal levels of thyrotropin only (Table 4).

Increasing levels of thyrotropin were associated with decreased all-cause mortality in both men (HR, 0.57; 95% CI, 0.38-0.85) and women (HR, 0.84; 95% CI, 0.68-1.03). Increasing levels of free thyroxine were associated with increased mortality in both men (HR, 1.32; 95% CI, 1.02-1.72) and women (HR, 1.18; 95% CI, 1.03-1.36).

During follow-up, 87 (42%) of the 209 participants died from cardiovascular causes, 119 (58%) died from noncardiovascular causes, and the primary cause of death was unknown for 3 participants. Increasing levels of thyrotropin were associated with a decreased risk of both cardiovascular (sex-adjusted HR, 0.66; 95% CI, 0.48-0.98) and noncardiovascular (sex-adjusted HR, 0.84; 95% CI, 0.66-1.07) mortality. Increasing levels of free thyroxine were associated with an increased risk of both cardiovascular (sex-adjusted HR, 1.26; 95% CI, 1.05-1.52) and noncardiovascular (sex-adjusted HR, 1.10; 95% CI, 0.93-1.32) mortality.

Conversion of Free Thyroxine to Free Triiodothyronine

Participants who survived until age 89 years had higher ratios of free triiodothyronine to free thyroxine at baseline compared with the participants who died during follow-up (mean [SD], 0.25 [0.05] vs 0.23 [0.05]; independent *t* test, $P<.001$). This indicates an increased peripheral 5′deiodination activity in those participants who survived at least 4 years.

Low Free Triiodothyronine Syndrome

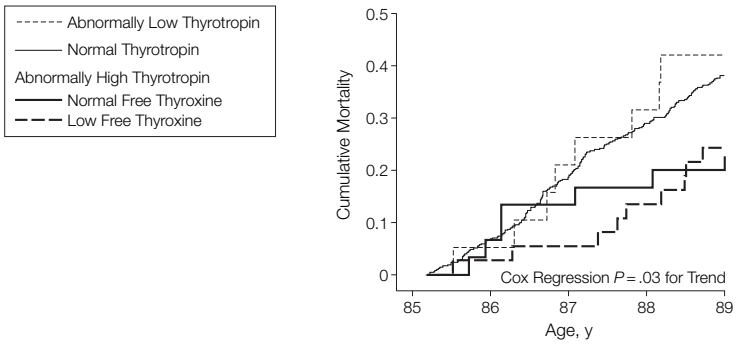
Decreasing levels of free triiodothyronine were associated with poor outcome on virtually all domains of functional performance at baseline (Table 3). Low levels of free triiodothyronine also were associated with an accelerated increase of disability in ADLs, disability in instrumental ADLs, and depressive symptoms during follow-up, and with an accelerated decline of global cognitive function (Table 3). Decreasing levels of free triiodothyronine were associated with increased mortality; the sex-adjusted HR per SD decrease of free triiodothyronine of 35.7 pg/dL (0.55 pmol/L) was 1.31 (95% CI, 1.15-1.52; $P<.001$). However, this association disappeared after adjustment for baseline disability and health status (HR, 1.05; 95% CI, 0.91-1.20; $P=.50$).

To study whether levels of free thyroxine and free triiodothyronine were independent predictors of mortality, the risks of mortality of free triiodothyronine and free thyroxine were estimated simultaneously, with adjustments for baseline disability and health status. In this model, the increased mortality associated with increasing baseline level of free thyroxine was independent of the level of free triiodothyronine. The HR per SD increase of free thyroxine was 1.18 (95% CI, 1.05-1.33; $P=.005$). The HR per SD decrease of free triiodothyronine, however, decreased to 1.10 (95% CI, 0.95-1.27; $P=.20$).

Specific Medication

All analyses described above were repeated after exclusion of the 21 participants who took medication for thyroid disease at baseline. In these restricted analyses, there were marginal significant findings on the performance of instrumental ADLs and the immediate word learning test. Increas-

Figure 2. Cumulative Mortality of Participants Based on Clinical Stratification of Thyroid Status



Abnormally Low Thyrotropin	19	18	15	13	11
Normal Thyrotropin	472	441	385	335	287
Abnormally High Thyrotropin					
Normal Free Thyroxine	30	28	26	25	23
Low Free Thyroxine	37	36	35	32	28

Plasma thyrotropin levels below 0.3 mIU/L were considered to be abnormally low; levels above 4.8 mIU/L were considered to be abnormally high. Plasma free thyroxine levels below 1.01 ng/dL (13 pmol/L) were considered to be abnormally low; levels between 1.01 and 1.79 ng/dL (13 and 23 pmol/L) were considered to be normal.

Table 4. Risk of Mortality in Participants Aged 85 Years Based on Baseline Levels of Thyrotropin and Free Thyroxine (N = 558)

	Crude*	Adjusted†	Participants With Normal Thyrotropin Levels Only (n = 472)‡
Thyrotropin			
HR (95% CI)	0.76 (0.62-0.92)‡	0.77 (0.63-0.94)	0.91 (0.79-1.00)
P Value	.005	.009	.17
Free thyroxine			
HR (95% CI)	1.22 (1.08-1.37)‡	1.16 (1.04-1.30)	1.25 (1.09-1.43)
P Value	.001	.009	.001

*Sex-adjusted HRs for mortality were estimated using Cox regression and are presented per SD increase of 2.71 mIU/L for thyrotopin and 0.21 ng/dL (2.67 pmol/L) for free thyroxine.
†Adjusted for baseline disability and health status (including levels of albumin and C-reactive protein, Mini-Mental State Examination score, number of chronic diseases, and subjective health).
‡Have thyrotropin plasma levels between 0.3 and 4.8 mIU/L.

ing levels of thyrotropin were associated with a lower increase of disability during follow-up (additional annual change, β, –0.14 [SE, 0.06]; *P*=.02) and with better memory during follow-up (additional annual change, β, 0.13 [SE, 0.06]; *P*=.03). The mortality risk per SD increase of thyrotropin at baseline was 0.78-fold lower (95% CI, 0.65-0.93; *P*=.006) whereas the mortality risk per SD increase of free thyroxine was 1.21-fold higher (95% CI, 1.07-1.37; *P*=.002).

COMMENT

In this prospective observational study of a population-based cohort of individuals aged 85 years, no consistent associations were found between thyroid status and ADLs, depressive symptoms, and cognitive performance, neither in the cross-sectional nor in the prospective analyses. In addition, we found that increasing levels of thyrotropin and decreasing levels of free thyroxine, both representing lower thyroid function, were associated with a survival benefit.

Performance

Both subclinical and overt thyroid dysfunction are supposed to have a negative effect on performance.[3,4] The absence of associations between thyroid status and various parameters of performance in this population of community-dwelling elderly is therefore unexpected. Although various cross-sectional studies have found associations between thyroid function, depressive symptoms, and cognitive decline,[24-28] thyroid function was not a risk factor for cognitive impairment or depressive symptoms, neither in the cross-sectional analysis, nor in the prospective analysis. It is unlikely that the study was underpowered to show differences in performance. For instance, the overall annual increase in ADL disability was estimated at 1.2 points per year. The additional annual change due to thyroid dysfunction was estimated at –0.01 points per SD increase of thyrotropin at baseline (95% CI, –0.11 to 0.09 points). The corresponding 95% CI indicates that larger effects on ADL disability than the reported range can be excluded. Effect sizes due to abnormal thyrotropin levels higher than 10% of the overall annual deterioration of ADL are thus unlikely. In a similar reasoning, given the small variance of the risk estimates and the considerable deterioration in performance after age 85 years, additional worsening due to thyroid dysfunction higher than 10% (disability and global cognitive function) and 20% (depressive symptoms) can be excluded.

On the other hand, one may argue that we have not separated participants with biochemical thyroid dysfunction with accompanying symptoms from those who had biochemical signs of thyroid dysfunction only. However, when studying the relationship between thyroid function and clinical symptoms, it is essential to uncouple biochemical features from clinical features. For the present analyses we have defined subclinical thyroid dysfunction as those with abnormal levels of thyrotropin but normal levels of free thyroxine, whereas participants with overt thyroid dysfunction have abnormal levels of both. These definitions are in line with the recent consensus statement.[3]

Thyroid dysfunction, disability, depressive symptoms, and cognitive impairment are prevalent in old age. Therefore, primary care physicians will face a considerable number of elderly individuals who have a combination of these disorders. This explains that a relatively high proportion of elderly individuals with disability, depressive symptoms, or cognitive impairment who are screened will have biochemical evidence of thyroid dysfunction. The classic reasoning is that this thyroid dysfunction causes these disorders. However, our data indicate that for most of these patients it is unlikely that the thyroid dysfunction is causal. The alternative explanation is that the abnormal thyroid dysfunction is just co-occurring with all of these disorders.

Survival

In 1928, Robertson[28] reported that mice fed with desiccated thyroid throughout their life had a shorter life span than control mice. In addition, rats fed with thyroxine did not live as long as controls[29]; and Wistar rats with experimental hypothyroidism had significantly longer life spans than normal rats.[30] Moreover, Ames and Snell dwarf mice with undetectable levels of pituitary hormones (prolactin, growth hormone, and thyrotropin) due to genetic mutations have a 50% to 64% prolonged life span compared with their age-matched wild-type littermates.[31-33] From a biological point of view, our finding that decreased levels of free thyroxine are associated with longer life span is expected. Our findings are also in line with an earlier study in elderly individuals that found a single measurement of low serum thyrotropin to be associated with increased rates of mortality from all causes.[34] These data contrast with a recent study in middle-aged participants in which males with subclinical hypothyroidism have a higher rate of mortality from all causes, the risk being absent in women.[35] The latter finding indicates that consequences of thyroid dysfunction during middle age cannot be extrapolated to old age, and vice versa.

It is tempting to speculate on how or why abnormal high thyrotropin levels are associated with lower all-cause mortality. Lower metabolic rate is related with increased survival in several species[36] and it may be suggested that a lower metabolic rate underlies the lower mortality in humans with decreased free thyroxine. Moreover, caloric restriction is known to prolong life in rodent models, an effect that may be the result of lower thyroid function and a lower metabolic rate.[37-39] It is not known whether mild hypothyroidism in elderly individuals, commonly caused by autoimmune thyroiditis, has a similar effect on metabolism. Outcomes from clinical experiments comparing substitution therapy are needed to judge whether this interpretation is correct.

Low Triiodothyronine Syndrome

For many years, thyroid dysfunction and mortality have been coupled in the low triiodothyronine syndrome, which

is found in patients with serious nonthyroidal illnesses.[40-43] These low levels of triiodothyronine are thought to be the consequence of a decreased conversion of thyroxine into triiodothyronine by a lower capacity or a lower amount of 5′selenodeiodinase in peripheral tissues due to disease-related factors.[44,45] In our study, we found significant associations between low levels of free triiodothyronine, poor performance, and increased mortality. The association between free triiodothyronine and mortality disappeared when we adjusted for baseline disability and health status. Moreover, this association also disappeared when we simultaneously estimated the effects of both free thyroxine and free triiodothyronine on mortality in 1 model. The finding that the increased mortality risk for higher free thyroxine was independent of the level of free triiodothyronine indicates that the association between free thyroxine and mortality was not explained by an underlying low triiodothyronine syndrome.

Strengths and Weaknesses

The strength of the present study is that it seems to reflect the natural history of elderly individuals with different thyroid function given the population-based character and 87% enrollment of the 85-year olds, the few number of individuals who were lost to follow-up, the fact that specific therapeutic interventions were seldom, and the annual repeated measurements of performance. The weakness is that it relies on a single baseline assessment of thyroid function with a repeated measurement available only at age 88 years. Moreover, because of the observational nature of the data we cannot exclude that residual confounding is at play and therefore we are not able to draw final conclusions on causality.

Clinical Implications

Abnormal levels of thyrotropin are often found in elderly individuals, as are disturbances in mood, cognitive function, and cardiovascular risk factors. A commonly used explanation is that the latter are adverse effects of (subclinical) thyroid dysfunction. The data presented herein argue against a causal interpretation. Therefore, we believe that thyroid substitution therapy in older individuals with abnormally high thyrotropin levels is unlikely to be beneficial and may even be harmful. Our observations in the relatively small subgroup with abnormally low levels of thyrotropin suggest that treatment of high thyroid function might lead to better survival without threatening performance in daily living.

Conclusion

In the general population of the oldest old, we found no association between levels of thyrotropin and performance. Moreover, elderly individuals with abnormally high levels of thyrotropin were found to have a prolonged life span. Hence, current clinical practice of treating these elderly persons may have limited clinical benefit. Final proof for not treating elderly individuals with abnormally high thyrotropin levels can only come from a well-designed randomized placebo-controlled clinical trial.

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Study concept and design: Gussekloo, van Exel, de Craen, Meinders, Westendorp.
Acquisition of data: Gussekloo, van Exel, Frölich, Westendorp.
Analysis and interpretation of data: Gussekloo, van Exel, de Craen, Frölich, Westendorp.
Drafting of the manuscript: Gussekloo, Westendorp.
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