Thyroid Function and General Health

CHAPTER 3.1

THYROID FUNCTION ASSOCIATED WITH FRAILTY INDEX, A MEASURE OF FRAILTY AND GENERAL HEALTH

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ABSTRACT

Background Thyroid hormones affect metabolism in various tissues, organs and systems. However, the overall impact of thyroid function on an individual's vulnerability to adverse outcomes remains unclear. We therefore aimed to investigate the cross-sectional and prospective association of thyroid function with frailty index, a well-established measure of overall health, in a population-based, prospective cohort study.

Methods Participants of the Rotterdam Study with baseline measurements of thyroid function and frailty index were eligible. The frailty index was measured at baseline and after a median follow-up time of 10.1 (interquartile range, 5.7 to 10.8) years. A higher frailty index indicated a worse health state. We assessed the association of thyroid function with frailty at baseline, frailty at follow-up, and frailty changes over time, adjusting for age, sex, cohort, smoking, alcohol intake, and education.

Results We included 9640 participants (mean age, 64.9 years). There was a U-shaped association of TSH (*P* value, 0.0003) and FT_4 (*P* value, <0.0001) with frailty at baseline. There was no association of TSH, but a positive association of FT_4 with frailty at follow-up and frailty changes over time (β, 1.22; 95% confidence interval, 0.73 to 1.72 per 1 unit FT_4).

Conclusions In this population-based study, participants with low and high thyroid function were more likely to be frail than participants with normal thyroid function. However, only those with higher FT_4 levels had an increased risk of becoming more frail over time. The identification of FT_4 as a potential marker of health deterioration could have future implications regarding the prediction and prevention of frailty.

INTRODUCTION

Frailty is a condition of reduced physiological reserves, decreased resistance to stressors and enhanced vulnerability to poor health outcomes, such as diseases, disability, falls, institutionalization and death.[1] With the aging of the population, the prevalence of frailty is expected to rise.[2] Therefore, various tools are being utilized to evaluate and identify vulnerable subjects.[3] One of the most common measurements is the frailty index, which has been validated as a robust predictor of adverse outcomes in many patient and community settings.[3-6] The frailty index, also known as the "multidomain phenotype", was developed to reflect the multidimensional and dynamic nature of frailty. It is composed of >30 items covering a broad range of health domains, and it is considered a useful tool to quantify overall health and its changes over time.[7,8]

Thyroid hormones, which are key regulators of metabolism, are likely to be implicated in the development of frailty.[9] So far, variations in thyroid hormone levels have been linked to alterations in cardiometabolic, cognitive and musculoskeletal functioning, which in turn contribute to a reduction in physiological capacity and resistance to stressors.[9] Most previous research, however, has focused on the system-specific effects of thyroid function, suggesting that lower thyroid hormone levels are associated with a higher risk of metabolic outcomes (ie, diabetes, dyslipidemia, and nonalcoholic fatty liver disease),[10-12] whereas higher thyroid hormone levels are associated with a higher risk of cognitive decline, atrial fibrillation, and osteoporosis.[13-17] Meanwhile, the overall impact of thyroid function on general health remains to be clarified. This could be important to further improve the prediction and prevention of health deterioration over time.

To date, only very few studies have investigated the association of thyroid function with frailty assessed either by the "physical phenotype" [18] or the Frail scale,[19] with inconsistent results. In a cross-sectional study assessing frailty by the Frail scale, higher free thyroxine (FT_4) levels were associated with an increased frailty risk, but there was no association for thyroid-stimulating hormone (TSH).[19] Another study assessing frailty by the "physical phenotype" showed that men with a low thyroid function (ie, highest TSH quintile) and women with a high thyroid function (ie, lowest TSH quintile) had an increased frailty risk.[18] Notably, both the Frail scale and the physical phenotype are derived from only 5 items mainly reflecting the physical aspect of frailty.[20,21] What previous research is lacking, however, is the utilization

of a multidimensional tool that would be able to capture the pleiotropic effects of thyroid hormones on general health.

Therefore, in a large population-based prospective study of middle-aged and elderly subjects, we aimed to investigate the cross-sectional and prospective association of thyroid function with the frailty index, a well-established measure of overall health.

METHODS

Study population

The Rotterdam Study is a prospective population-based cohort study that aims to investigate the determinants, occurrence, and progression of chronic diseases in the middle-aged and elderly. The objectives and study design have been described in detail previously.[22] The Rotterdam Study was initiated in 1989, including 7983 participants ≥55 years of age (RS I) residing in Ommoord district of Rotterdam, the Netherlands. In 2000, the study was extended with a second cohort of 3011 subjects (RS II). In 2006, a third cohort of 3932 subjects ≥45 years of age was added (RS III). Study participants undergo extensive follow-up medical examinations every 3 to 5 years.

For the current study, baseline measurements were performed during the third visit of the first cohort (n=4797) and the first visits of the second (n=3011) and third (n=3932) cohorts of the Rotterdam Study (Supplemental Figure 1). A total of 9640 participants with data available on thyroid function and frailty index at baseline were considered eligible. Of these, 6416 participants had repeated measurements on frailty index (Table 1).

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus University and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the Population Study Act Rotterdam Study. In accordance with the Declaration of Helsinki, all participants provided written informed consent.

Assessment of thyroid function

Thyroid function was assessed at baseline in three study cohorts using the same method and assay. Concentrations of TSH, FT_4, and thyroid peroxidase antibodies (TPOAbs) were measured on baseline serum samples stored at -80°C using the electrochemiluminescence immunoassay ECLIA Roche. The reference ranges of serum

Table 1. Baseline characteristics of 9640 participants*

	Total	Follow-up available	Died before follow-up	No follow-up available
Number	9640	6416	2364	860
Age, years	64.9 (9.7)	61.8 (7.8)	74.6 (8.4)	62.2 (8.6)
Women, n (%)	5467 (56.7)	3709 (57.8)	1233 (52.2)	525 (61)
Smoking, n (%)				
current	2042 (21.2)	1321 (20.6)	506 (21.4)	215 (25.0)
former	4549 (47.2)	3059 (47.7)	1124 (47.5)	366 (42.6)
never	3010 (31.2)	2018 (31.5)	714 (30.2)	278 (32.3)
Education, n (%)				
Elementary	1189 (12.3)	595 (9.3)	469 (19.8)	125 (14.5)
Lower secondary	3874 (40.2)	2555 (39.8)	957 (40.5)	362 (42.1)
Higher secondary	2787 (28.9)	1897 (29.6)	670 (28.3)	220 (25.6)
Tertiary	1720 (17.8)	1331 (20.7)	244 (10.8)	145 (16.9)
TSH, mIU/L, median (IQR)	1.9 (1.2-2.8)	1.9 (1.3-2.8)	1.8 (1.1-2.6)	1.9 (1.2-2.8)
FT_4, ng/dL	1.2 (0.1)	1.2 (0.1)	1.2 (0.2)	1.2 (0.1)
TPOAb positive, n (%)	1272 (13.2)	870 (13.6)	282 (11.9)	120 (14.0)
TPOAb, kU/ml, median (IQR)	7.6 (5.0-13.6)	7.7 (5.0-13.8)	6.5 (5.0-12.6)	8.7 (5.2-14.7)
Use of thyroid medication, n (%)	308 (3.2)	210 (3.3)	71 (3.0)	27 (3.1)
Thyroid surgery, n (%)	167 (1.7)	100 (1.6)	49 (2.1)	18 (2.1)
Frailty index†	17.1 (8.7)	15.0 (7.1)	22.7 (10.4)	16.7 (8.0)

*Data are mean (standard deviation), unless otherwise specified. †To increase the interpretability of the risk estimates, the frailty index score was multiplied by 100. Abbreviations: TSH, thyroid-stimulating hormone; IQR, interquartile range; FT_4, free thyroxine; TPOAb, thyroid peroxidase antibodies (cutoff 35 kU/ml).

TSH (0.40 to 4.0 mIU/L) and serum FT_4 (11 to 25 pmol/L; alternatively, 0.86 to 1.94 ng/dL) were determined based on national guidelines and our previous studies.[10,11,23] The time of blood sampling was recorded. 99% of the blood samplings were performed between 8.00 ^{AM} and 11.00 ^{AM}.

Assessment of frailty index

Frailty was assessed by the frailty index, which is defined as the accumulation of health deficits including symptoms, signs, diseases and functional impairments.[7] A 45-item frailty index has been recently validated in the Rotterdam Study and has been described extensively elsewhere.[5] In short, health deficits were selected using a stepwise procedure, on the basis of the following predefined criteria: (1) the deficit is associated with health; (2) the prevalence or severity of the deficit generally increases with age; (3) the deficit is not too exceptional (ie, prevalence <5 %) or too

common (ie, prevalence >80%).[4,5] In case of a high correlation between variables of the same domain (r >0.7), only the one with the highest correlation with age was eventually included in the score.[4,5] To be able to evaluate changes of frailty over time, we used a slightly adapted version of the Rotterdam Study frailty index score that consisted of 38 health-related variables covering various health domains, including functional status (n=13), health conditions (n=6), diseases (n=6), cognition (n=6), mood (n=4), and nutritional status (n=3).[24] The remaining 7 items (namely vitamin D, sex hormone binding globulin, mobility, uric acid, pro-B-type natriuretic peptide, C-reactive protein, and homocysteine) were not assessed at follow-up and were therefore removed from the original Rotterdam Study frailty index score.[24] To obtain a stable frailty index score, it is recommended to have data available on at least 20 items.[4] Therefore, participants of the Rotterdam Study with <20 observed items were excluded. For individuals with data available on ≥20 items, missing values were imputed using multiple imputation.[5] Deficits were dichotomized or categorized into a score ranging from 0 (deficit absent) to 1 (deficit present) (Supplemental Table 1). Per person, the frailty index score was calculated as the sum of present deficits divided by the total number of potential deficits. For instance, if 10 out of 38 deficits were present, the frailty index would be 10/38. A higher score of the frailty index indicated a worse health state. In order to increase the interpretability of our risk estimates, frailty index score was multiplied by 100.

Additional measurements

The baseline home interview provided extensive information on medical history, tobacco smoking, alcohol consumption, education level, and medication. Smoking habits were categorized as current, past, and never smoking. Education level was classified as low, intermediate, and high.

Statistical analysis

We performed ordinary least-squares linear regression, using restricted cubic splines with three knots to allow for potential nonlinearity. First, we cross-sectionally investigated the association of thyroid function (ie, TSH and FT_4 levels) with the frailty index at baseline. Second, we investigated the association of thyroid function with the frailty index at follow-up. Third, we prospectively investigated the association of thyroid function with changes in the frailty index over time (calculated by subtracting the frailty index at baseline from the frailty index at follow-up). Potential

confounders were selected on the basis of biological confounding plausibility. The first analysis was adjusted for age, sex, cohort, smoking status, alcohol intake, and education level. The second and third analyses were additionally adjusted for the frailty index at baseline and time interval between the measurements of the frailty index. To assess the potential role of thyroid autoimmunity on frailty, we also investigated the cross-sectional and prospective association of TPOAb with the frailty index, additionally adjusting for TSH or FT_4 levels. TSH and TPOAb values were logarithmically transformed, because of their skewed distribution. All models were tested for effect modification by separately adding product interaction terms of TSH, FT_4 or TPOAbs with each covariate of the multivariable model, but none of the interaction terms were significant.

Multiple imputations were performed for covariates with missing data (<5% for all covariates). Statistical analyses were performed using R statistical software (rms package, R project, Institute for Statistics and Mathematics, R Core Team, version 3.2.2) and SPSS version 21 (IBM SPSS).

Sensitivity analyses

We performed several analyses to test the robustness of our findings. (1) We reran the cross-sectional analysis using the original 45-item frailty index instead of the adapted frailty index. (2) We restricted the cross-sectional analysis to participants with both baseline and prospective data on the frailty index. (3) We restricted the cross-sectional and prospective analyses to: (i) participants without past thyroid surgery and not using thyroid medications; (ii) participants with thyroid function within the reference range, without past thyroid surgery and not using thyroid medications. (4) To address the issue of attrition, we used the inverse probability weighting method. We fitted two logistic regression models predicting the possibility of having follow-up data. The first model used as covariates the baseline frailty index, age, sex, cohort, smoking status, alcohol intake, education level, and TSH. The second model used as covariate only TSH. The stabilized weights for each participant were calculated as the predicted probability of the second model divided by that of the first model. Subsequently, we used the stabilized weights to examine the association of TSH with frailty changes over time. The analyses were also repeated for FT_4. (5) In our prospective analysis, we added product interaction terms of thyroid parameters with the frailty index at baseline to test for effect modification by the baseline health status of participants. (6) To explore a potential

influence of the time of blood sampling or thyroid autoimmunity on our results, our cross-sectional and prospective analyses were additionally adjusted for the time of blood withdrawal (recorded in hours and minutes) or TPOAb levels.

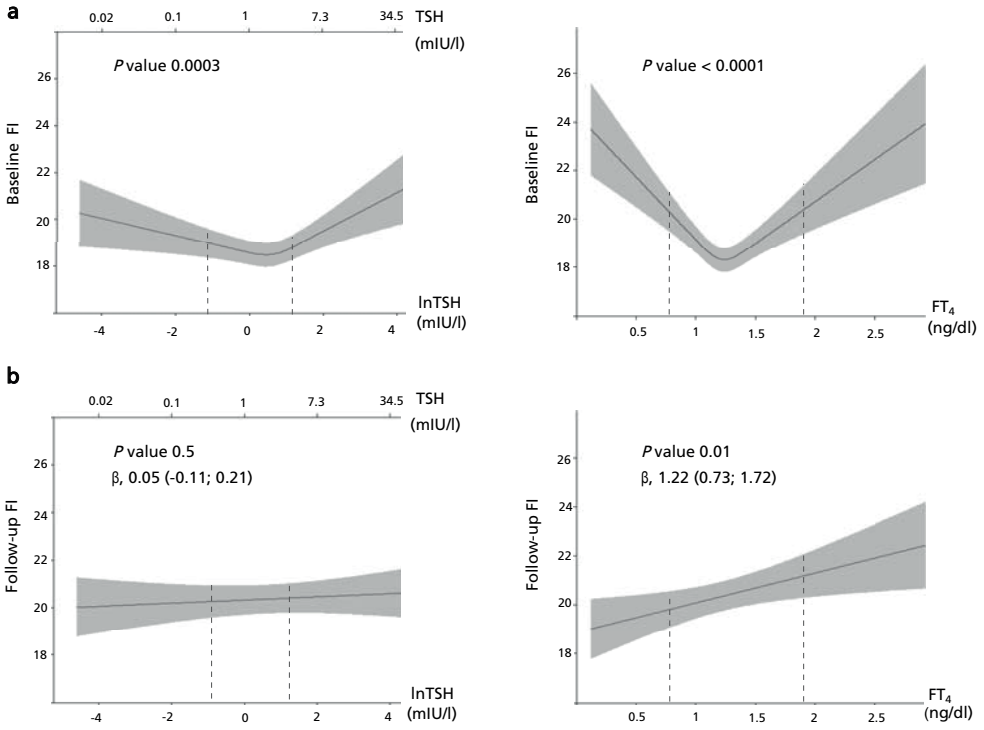
RESULTS

Baseline characteristics of 9640 eligible participants are shown in Table 1. The mean age was 64.9 years and 56.7% were women. The median TSH was 1.9 mIU/L, with an interquartile range of 1.2 to 2.8 mIU/L. Of participants, 3.0% had TSH below, 86.8% within, and 10.2% above the reference range. The mean (standard deviation) FT_4 was 1.2 (0.1) ng/dL. Of participants, 1.2% had FT_4 below, 98.4% within, and 0.4% above the reference range. The mean (standard deviation) frailty index was 17.1 (8.7), with a range of 0 to 66.4 (Table 1). After a median follow-up time of 10.1 (interquartile range, 5.7 to 10.8) years, the frailty index was remeasured in 6416 participants. Of participants, 2364 died before having a follow-up frailty measurement. The remaining 860 participants did not have complete follow-up data available on frailty (Table 1). The median TSH and mean FT_4 concentrations at baseline were very similar among participants who died, those with repeated measurements of frailty, and those without follow-up data available on frailty (Table 1). Participants with prospective data had a lower frailty index than those without prospective data (Table 1).

Cross-sectional analysis: thyroid function and frailty index at baseline

There was a U-shaped association of both TSH (*P* value, 0.0003) and FT_4 levels (*P* value, <0.0001) with the baseline frailty index (Figure 1a). Results remained similar after using the original 45-item frailty index (Supplemental Figure 2a), after excluding participants without prospective data on frailty (Supplemental Figure 2b), after excluding participants with known thyroid disease (Supplemental Figure 2c), and after additionally adjusting for the time of blood withdrawal or TPOAb levels. Among euthyroid participants, there was a U-shaped association of FT_4 with frailty index (*P* value, <0.0001), but no association of TSH with frailty index (*P* value, 0.3) (Supplemental Figure 3a).

Figure 1. Association of thyroid function with the frailty index.



a. Cross-sectional association of thyroid function with frailty index at baseline (TN, 9640); b. Association of thyroid function with the frailty index at the end of the follow-up (TN, 6416). We used linear regression models with restricted cubic splines. Predicted means of frailty index (black lines) with 95% confidence intervals (gray areas) are plotted against TSH and FT_4 concentrations. Dashed lines indicate the limits of TSH or FT_4 reference ranges. A higher value of frailty index represents a worse health state. *P* values are for the plotted association. Abbreviations: TSH, thyroid-stimulating hormone; FT_4, free thyroxine; FI, frailty index, TN, total number.

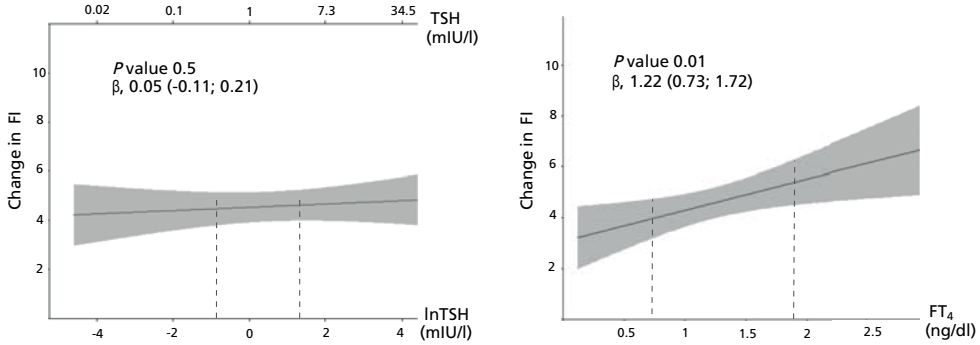
Thyroid function and frailty index at follow-up

TSH was not associated with frailty index at follow-up (β, 0.05; 95% confidence interval [95% CI], -0.11 to 0.21 per 1 unit logTSH) (Figure 1b). Increasing FT_4 levels were associated with a higher frailty index at follow-up (β, 1.22; 95% CI, 0.73 to 1.72 per 1 unit FT_4) (Figure 1b).

Prospective analysis: thyroid function and changes in frailty index

There was no association of TSH (β, 0.05; 95% CI, -0.11 to 0.21 per 1 unit logTSH) and a positive association of FT_4 with frailty changes over time (β, 1.22; 95% CI, 0.73 to 1.72 per 1 unit FT_4; Figure 2). Results remained similar after excluding participants with known thyroid disease (Supplemental Figure 2d), after additionally adjusting

Figure 2. Prospective association of thyroid function with changes in the frailty index.



Total number, 6416. Changes in the frailty index were calculated by subtracting the frailty index at baseline from the frailty index at follow-up. We used linear regression models with restricted cubic splines. Predicted means of frailty index (black lines) with 95% confidence intervals (gray areas) are plotted against TSH and FT_4 concentrations. Dashed lines indicate the limits of TSH or FT_4 reference ranges. A higher value of frailty index represents a worse health state. *P* values are for the plotted association. Abbreviations: TSH, thyroid-stimulating hormone; FT_4, free thyroxine; FI, frailty index.

for the time of blood withdrawal or TPOAb levels. The association became stronger after the inverse probability weighting (β, 0.19; 95% CI, -0.03 to 0.42 per 1 unit logTSH; β, 1.99; 95% CI, 0.97 to 3.0 per 1 unit FT_4). Among euthyroid participants, the association was not statistically significant (β, 0.18; 95% CI, -0.11 to 0.48 per 1 unit logTSH; β, 1.0; 95% CI, -0.17 to 2.18 per 1 unit FT_4) (Supplemental Figure 3b). Also, the interaction terms of TSH and FT_4 with the frailty index at baseline were not statistically significant.

TPOAb and frailty index

In the cross-sectional analysis, TPOAb were not associated with frailty index (β, -0.01; 95% CI,-0.15 to 0.13 per 1 unit logTPOAb; Supplemental Figure 4). In the prospective analysis, there was an inverse U-shaped association of TPOAb with frailty changes over time (*P* value, 0.0002; Supplemental Figure 4). Results remained similar after additionally adjusting for TSH or FT_4.

DISCUSSION

In this large population-based cohort study, participants with low and high thyroid function were more likely to be frail than participants with normal thyroid function.

However, only those with higher FT_4 levels had an increased risk of becoming more frail over time.

Thyroid hormones exert pleiotropic effects on nearly all organs and systems,[9,10,12-14] the resultant of which can be reflected in overall health. However, whereas most previous research has focused on the system-specific effects of thyroid function,[13,14,16,17,23,25-27] our study provides novel insights into the impact of thyroid function on general health. Most importantly, our findings suggest that high circulating FT_4 levels can contribute to health deterioration over time. This can be attributed to the combination of many deleterious system-specific effects of excess thyroid hormones, as arrhythmias, hemodynamic changes, hypercoagulability, neurodegeneration, and reduction in bone mineral density. In line, large prospective population-based studies have reported that subjects with high FT_4 levels have an increased risk of developing a broad range of adverse outcomes, including atrial fibrillation, chronic kidney disease, age-related macular degeneration, dementia, osteoporosis, and fractures.[13,14,16,17,25,26] A more general pathway linking high thyroid function to frailty could be related to the perturbation of the prooxidant-antioxidant balance.[28,29] Excess circulating thyroid hormones stimulate the production of reactive oxygen species via accelerating basal metabolism and increasing oxygen consumption.[30] In turn, reactive oxygen species predispose to altered gene expression, mitochondrial dysfunction, and cumulative cellular damage,[31] which increase the susceptibility to physical, cognitive, and functional decline. Conversely, low thyroid function can reduce the frailty risk via decreasing basal metabolic rate and promoting energy conservation.[32] As shown in experimental research, age-related chronic disorders occur less often in the mutant hypothyroid dwarf mice than in the wild-type mice.[33]

Thyroid autoimmunity could additionally be involved in the development of frailty. To date, the association of thyroid autoimmunity with frailty risk has been investigated in only one population-based study, reporting a low frailty risk in TPOAb-positive women.[34] However, this study was cross-sectional, assessed frailty by the physical phenotype and included only women aged ≥65 years of age (n=641). We addressed some limitations of this study, by exploring the prospective association of TPOAb levels with the risk of frailty assessed by the multidomain phenotype, in a much larger population of >6000 middle-aged and elderly men and women (n=6416). Our results point toward the possibility of protective autoimmunity [35] and

confirm that the association of TPOAbs with frailty risk is independent of thyroid function.

During follow-up, the frailty risk increased with higher FT_4 levels. Based on the negative feedback mechanism of the hypothalamus-pituitary-thyroid axis, one would expect an increased frailty risk with lower TSH levels. However, TSH was not associated with frailty risk in our study. Similarly, many other population-based cohort studies have suggested that in middle-aged and elderly subjects, FT_4 rather than TSH levels can predict various adverse outcomes, including atrial fibrillation, dementia and mortality.[15,27,36] These observations may reflect an alteration in the TSH-FT_4 set point of the negative feedback mechanism, due to the ageing process.[37] After restricting the study population to euthyroid participants, the association of thyroid function with frailty risk attenuated and/or lost statistical significance. This suggests that elevated levels of FT_4 have a larger effect on frailty risk over time as compared to FT_4 levels within the reference range.

Our cross-sectional and prospective analyses examined the relationship of thyroid function with the likelihood of being frail and the risk of becoming more frail over time, respectively. Cross-sectional designs, however, do not provide evidence on the temporal relationship between the exposure and outcome. Therefore, the results of our cross-sectional analysis may be partly influenced by reverse causation. In other words, health-related problems underlying a high frailty index can potentially alter thyroid function parameters. Notably, our participants with low thyroid function had an increased likelihood of being frail, but did not have an increased risk of becoming more frail over time. This can be explained by the condition of non-thyroidal illness syndrome, which is typically characterized by low thyroid hormones and normal TSH levels, secondary to a poor health status.[38]

Alternatively, the discrepancy between our cross-sectional and prospective findings could have been explained by the selective dropout of participants with low thyroid function. This is unlikely, given that the median TSH levels and the mean FT_4 levels among participants with prospective data were similar to those without prospective data. Another important issue is whether the participants of our prospective analysis were representative of the baseline sample population. Indeed, participants with prospective data had a lower baseline frailty index than did those without prospective data, which indicates that the more frail participants at baseline may have died during follow-up. However, we do not expect our conclusions to be compromised by the selective dropout of frail participants for several reasons.

First, we obtained consistent results after restricting our cross-sectional analyses to participants with complete follow-up data on the frailty index. Second, the product interaction term of thyroid function with the frailty index at baseline was not statistically significant, suggesting that our prospective findings were independent of the baseline health status of participants. Third, we addressed the issue of attrition by using the inverse probability weighting method. Originally, the effect of FT_4 on frailty seemed to wane over time, as it was smaller in the prospective than in the cross-sectional analysis. However, the effect of FT_4 on frailty became stronger after the inverse probability weighting, indicating that the selective dropout of participants may have led to an underestimation rather than an overestimation of our prospective results.

To the best of our knowledge, this is the first population-based cohort study that explores the relationship of thyroid function with the frailty index. The latter represents a well-validated frailty measure that is considered useful to evaluate overall health and trajectories of health over time.[3] Our frailty index data were available at two time points with a long follow-up time interval, allowing us to explore the relation between thyroid function variations and health changes over time. The frailty index characteristics of our population were similar to most other populations of similar age.[4,6,39] Moreover, our study is the largest investigation on thyroid function and frailty. The large sample size enabled us to perform multiple sensitivity analyses. Additionally, to our knowledge, our study is the first to examine the prospective association of TPOAb levels with frailty risk. Other strengths include the well-characterized population-based study sample, the laboratory assessment of thyroid parameters and the available data on potential confounding factors.

Several limitations should also be mentioned. Considering the observational character of our study, one can argue that reverse causation may have affected even our prospective findings. This is very unlikely, given that non-thyroidal illness syndrome is typically characterized by low thyroid hormones;[38] whereas we found an increased frailty risk among participants with high rather than low FT_4 levels. Moreover, we did not have repeated measurements of thyroid function. This, however, would tend to underestimate the association between thyroid function and frailty risk, based on the low intra-individual variability of TSH and FT_4 levels.[40] Also, we did not measure serum triiodothyronine levels. Nevertheless, TSH and FT_4 are considered the most relevant measurements of thyroid function in clinical practice. In certain circumstances (eg, pregnancy or critical illnesses), substances interfering

with the FT_4 immunoassay can alter the affinity of thyroid hormones to plasma proteins. In our study, there were no data available on thyroid hormone-binding proteins. However, the concentrations of these proteins were most likely unaltered, given that our population consists of community-dwelling middle-aged and elderly individuals. Moreover, the possibility of residual confounding cannot be ruled out, even though we adjusted for various potential confounders. Lastly, our findings require confirmation in other ethnicities, given that the Rotterdam Study includes predominantly white participants.

Conclusions

In this large population-based cohort study, participants with low and high thyroid function are more likely to be frail than are participants with normal thyroid function. However, only those with higher FT_4 levels have an increased risk of becoming more frail over time. Our study provides novel insights into the possible impact of thyroid function on overall health, suggesting that elevated circulating FT_4 levels can constitute a useful marker of health deterioration. Therefore, our findings may have future implications regarding the prediction and prevention of frailty. Further studies are warranted to replicate our results in other population settings.

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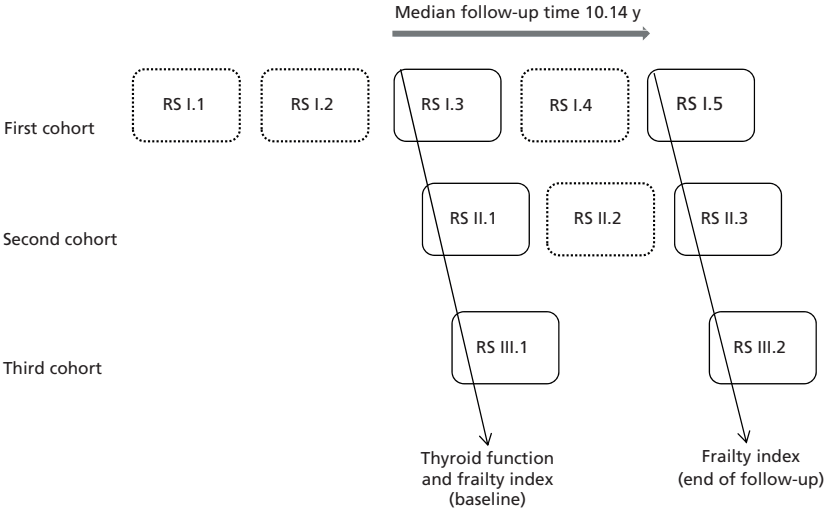
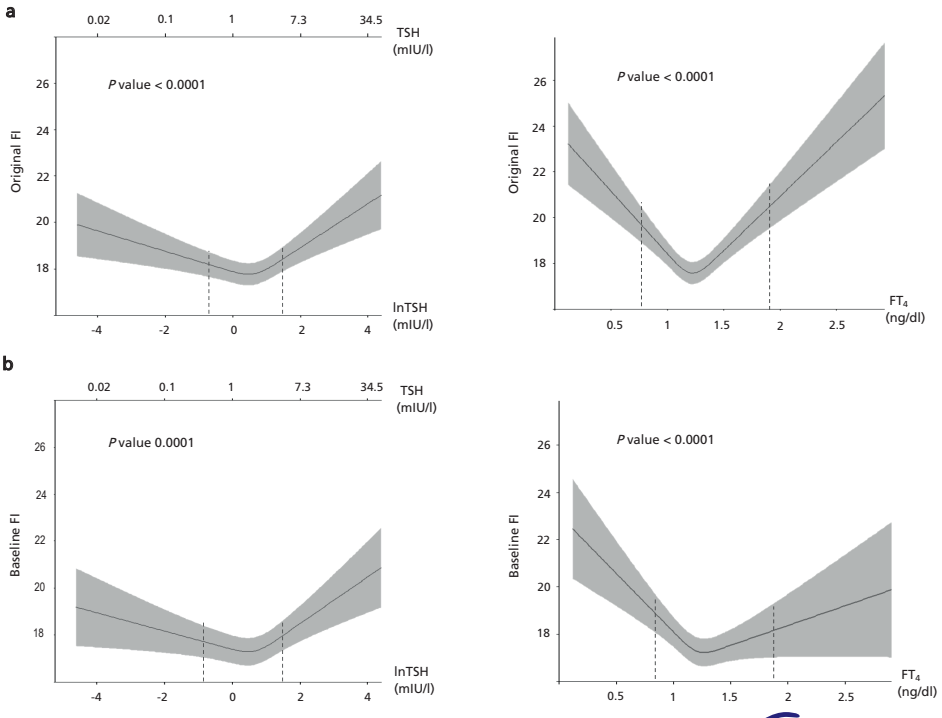
SUPPLEMENTAL MATERIAL

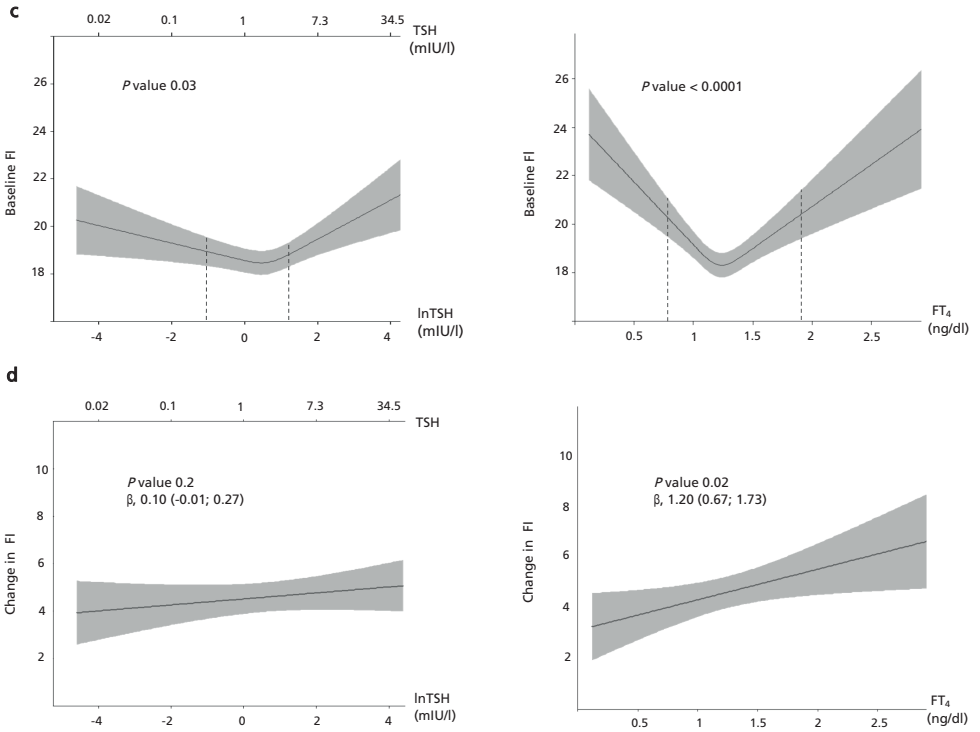
Supplemental Figure 1. Measurements of thyroid function and frailty index.



Thyroid function and frailty index were measured at baseline, during the first visit of the third cohort (RS I.3), the first visits of the second and third cohorts (RS II.1, RS III.1). Frailty index was remeasured at the end of the follow-up, during the fifth visit of the first cohort (RS I.5), the third visit of the second cohort (RS II.3) and the second visit of the third cohort (RS III.2). Abbreviation: RS, Rotterdam Study.

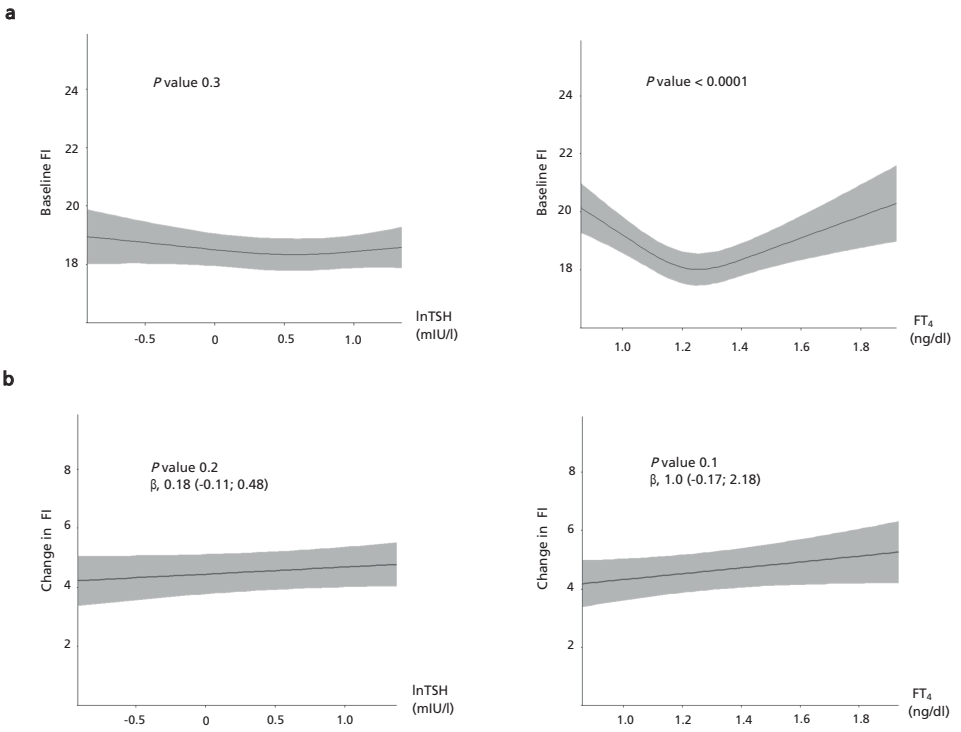
Supplemental Figure 2. Sensitivity analyses.





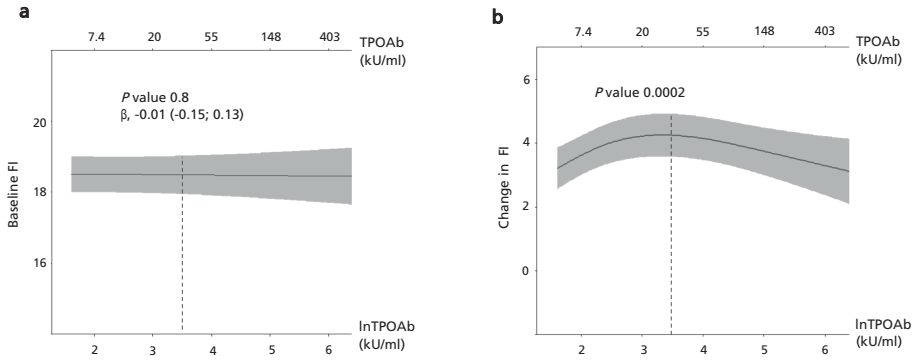
a. Cross-sectional association of thyroid function with original frailty index score (TN, 9640); b. Cross-sectional association of thyroid function with frailty index, restricted to participants with follow-up data on frailty index (TN, 6416); c. Cross-sectional association of thyroid function with frailty index at baseline, after excluding participants with past thyroid surgery and users of thyroid medication (TN, 9199); d. Prospective association of thyroid function with changes in frailty index, after excluding participants with past thyroid surgery and users of thyroid medication (TN, 6126). The changes in frailty index were calculated by subtracting the frailty index at baseline from frailty index at follow-up. We used linear regression models with restricted cubic splines. Predicted means of frailty index (black lines) with 95% confidence intervals (gray areas) are plotted against TSH and FT_4 concentrations. Dashed lines indicate the limits of TSH or FT_4 reference ranges. A higher value of frailty index represents a worse health state. *P* values are for the plotted association. Abbreviations: TSH, thyroid-stimulating hormone; FT_4, free thyroxine; FI, frailty index; TN, total number.

Supplemental Figure 3. Association of thyroid function with frailty index among euthyroid participants.



a. Cross-sectional association of thyroid function with frailty index at baseline (TN, 8038); b. Prospective association of thyroid function with changes in frailty index (TN, 5403). The changes in frailty index were calculated by subtracting the frailty index at baseline from frailty index at follow-up. We used linear regression models with restricted cubic splines. Predicted means of frailty index (black lines) with 95% confidence intervals (gray areas) are plotted against TSH and FT_4 concentrations. A higher value of frailty index represents a worse health state. *P* values are for the plotted association. Abbreviations: TSH, thyroid-stimulating hormone; FT_4, free thyroxine; FI, frailty index; TN, total number.

Supplemental Figure 4. Association of TPOAb with frailty index.



a. Cross-sectional association of TPOAb with frailty index at baseline (TN, 9640); b. Prospective association of TPOAb with changes in frailty index (TN, 6416). The changes in frailty index were calculated by subtracting the frailty index at baseline from frailty index at follow-up. We used linear regression models with restricted cubic splines. Predicted means of frailty index (black lines) with 95% confidence intervals (gray areas) are plotted against TPOAb concentrations. A higher value of frailty index represents a worse health state. Dashed lines indicate the cutoff of TPOAb positivity (35 kU/ml). *P* values are for the plotted association. Abbreviations: TPOAb, thyroid peroxidase antibodies; FI, frailty index; TN, total number.

Supplemental Table 1. Items of the frailty index score

	Items	Additional information on the items	Cutoff values
1	Dressing and grooming [a]	Able to get the clothes from closets or drawers; able to dress; able to shampoo the hair; able to comb the hair or do the make up	without any difficulty = 0; with some difficulty = 0.33; with much difficulty = 0.66; unable to do = 1
2	Arising [a]	Able to stand up from a straight chair without using the arms for support; able to get in and out of bed	without any difficulty = 0; with some difficulty = 0.33; with much difficulty = 0.66; unable to do = 1
3	Eating [a]	Able to cut meat; able to lift a full cup or glass to the mouth; able to open a new carton of milk	without any difficulty = 0; with some difficulty = 0.33; with much difficulty = 0.66; unable to do = 1
4	Walking [a]	Able to walk outdoors on flat ground; able to climb up five steps	without any difficulty = 0; with some difficulty = 0.33; with much difficulty = 0.66; unable to do = 1
5	Hygiene [a]	Able to wash and dry the entire body; able to take a shower or bath	without any difficulty = 0; with some difficulty = 0.33; with much difficulty = 0.66; unable to do = 1
6	Reach [a]	Able to reach and get down a 1 kg object from just above the head; able to bend down to pick up clothing from the floor	without any difficulty = 0; with some difficulty = 0.33; with much difficulty = 0.66; unable to do = 1
7	Grip [a]	Able to open a car door; able to open jars which have been previously opened	without any difficulty = 0; with some difficulty = 0.33; with much difficulty = 0.66; unable to do = 1
8	Riding a bike [b]	Able to ride a bike	without any difficulty = 0; with some difficulty = 0.33; with much difficulty = 0.66; unable to do = 1
9	Telephone [b]	Able to use the telephone	without any difficulty = 0; with some difficulty or using a customized phone = 0.33; with much difficulty = 0.66; unable to do = 1
10	Meal [b]	Able to prepare meals	without any difficulty = 0; with some difficulty = 0.33; with much difficulty = 0.66; unable to do = 1
11	Gardening [b]	Able to maintain a garden	without any difficulty = 0; with some difficulty = 0.33; with much difficulty = 0.66; unable to do = 1
12	Landry [b]	Able to do the laundry	without any difficulty = 0; with some difficulty = 0.33; with much difficulty = 0.66; unable to do = 1
13	Financial [b]	Able to do finances	without any difficulty = 0; with some difficulty = 0.33; with much difficulty = 0.66; unable to do = 1
14	Depressed affect [c]	I felt that I could not shake off the blues even with help from family or friends; I felt depressed; I thought my life had been a failure; I felt lonely; I had crying spells; I felt sad	rarely or none of the time = 0; some or a little of the time = 0.33; occasionally or a moderate amount of time = 0.66; most or all of the time = 1

Supplemental Table 1. Items of the frailty index score (continued)

	Items	Additional information on the items	Cutoff values
15	Positive affect [c]	I felt that I was just as good as other people; I felt hopeful about the future; I was happy; I enjoyed life	rarely or none of the time = 1; some or a little of the time = 0.66; occasionally or a moderate amount of time = 0.33; most or all of the time = 0
16	Somatic and retarded activity [c]	I did not feel like eating; my appetite was poor; I had trouble keeping my mind on what I was doing; I felt that everything I did was an effort; I felt fearful; my sleep was restless; I talked less than usual; I could not get going	rarely or none of the time = 0; some or a little of the time = 0.33; occasionally or a moderate amount of time = 0.66; most or all of the time = 1
17	Interpersonal [c]	I was bothered by things that usually don't bother me; people were unfriendly; I felt that people dislike me	rarely or none of the time = 0; some or a little of the time = 0.33; occasionally or a moderate amount of time = 0.66; most or all of the time = 1
18	Falling	How often did you fall over the past 12 months?	no falling = 0; less than once a month = 0.5; more than once a month = 1
19	Joint complains	Did you have joint pain or other complaints from the knees, hips, back or hands?	no = 0; yes = 1
20	Forgetfulness	Do you sometimes forget what you were about to do?	no = 0; yes = 1
21	Aphasia	Do you have difficulties finding the right words?	no = 0; yes = 1
22	Liver enzymes [d]	Aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase	all values within the range = 0; abnormal values = 1
23	Creatinine [d]		Males: 65-115 µmol/L = 0; other values = 1 Females: 55-90 µmol/L = 0; other values = 1
24	Hyperlipidemia [d]		statin use and/or cholesterol levels >6.5 mmol/L; no statin use and cholesterol levels 2.9-6.5 mmol/L
25	High density lipoprotein [d]		values ≥1.55 = 0; values <1.55 = 1
26	Systolic blood pressure [d]	Measured three times, average was taken	values 90-140 = 0; values 140-160 = 0.5; values <90 = 0.5; values >160 = 1
27	Mini Mental State Examination		unimpaired >25 = 0; impaired ≤25 =1
28	Letter-Digit Substitution Test	The number of correct digits	above the mean or less than 1 sd below the mean = 0; 1 sd below the mean = 0.5; 2 sd below the mean = 1
29	Stroop test		above the mean or less than 1 sd above the mean = 0; 1 sd above the mean = 0.5; 2 sd above the mean = 1
30	Word Fluency test		above the mean or less than 1 sd below the mean = 0; 1 sd below the mean = 0.5; 2 sd below the mean = 1
31	Cancer		no = 0; yes = 1
32	Lung condition (COPD/Asthma)		no = 0; yes = 1

Supplemental Table 1. Items of the frailty index score (continued)

	Items	Additional information on the items	Cutoff values
33	Coronary heart disease	Prevalent coronary heart disease	no = 0; yes = 1
34	Stroke	Prevalent stroke	no = 0; yes = 1
35	Diabetes mellitus		no = 0; high glucose levels= 0.5; yes = 1
36	BMI	BMI < 18.5 = underweight BMI ≤25 and ≥18.5 = normal weight BMI <25 and ≤30 = overweight BMI <30 = obese	normal weight = 0; overweight = 0.5; obese or underweight = 1
37	Hospital admission	Last 12 months	no = 0; yes = 1
38	Age-related macular degeneration	Fundus photography after pharmacologic mydriasis. The eyes of each participant were graded and classified separately. The eye with the more severe grade was used to classify the person.	0 = 5-year risk of developing advanced age-related macular degeneration in at least one eye is 0.5%; 0.25 = 5-year risk is 3%; 0.50 = 5-year risk is 12% ; 0.75 = 5-year risk is 25%; 1= 5-year risk is 50%

The original frailty index score, which was designed and validated among 11539 participants of the RS, consisted of 45 variables. However, 7 items from the original RS frailty index (namely vitamin D, sex hormone binding globulin, mobility, uric acid, proBNP, C-reactive protein and homocysteine) were not assessed at follow-up. In order to assess frailty changes over time, these items were removed, resulting in an adapted RS frailty index that consisted of the remaining 38 health-related variables. Sources: [a] Stanford Health Assessment Questionnaire; [b] Lawton Instrumental Activities of Daily Living scale; [c] The CESD scale: a self-report depression scale; [d] Serum blood measurement; cutoff values derived from the Laboratory guide Erasmus Medical Center Rotterdam. Abbreviations: sd, standard deviation; RS, Rotterdam Study; BMI, body mass index.

CHAPTER 3.2

IDENTIFICATION OF GAIT ASPECTS RELATED TO THYROID FUNCTION

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Adapted from ***Sci Rep.*** *2016;6:38912*

ABSTRACT

Background Gait is an important health indicator and poor gait is strongly associated with disability and risk of falls. Thyroid dysfunction is suggested as a potential determinant of gait deterioration, but this has not been explored in a population-based study.

Methods We therefore investigated the association of thyroid function with gait patterns in 2645 participants from the Rotterdam Study with data available on TSH (thyroid-stimulating hormone), FT_4 (free thyroxine), and gait, without known thyroid disease or dementia. The primary outcome was global gait (standardized Z score), while secondary outcomes included gait domains (rhythm, variability, phases, pace, base of support, tandem, turning), and velocity. Gait was assessed by electronic walkway.

Results Multivariable regression models revealed an inverted U-shaped association of TSH (*P* value, <0.001), but no association of FT_4 concentrations with global gait (*P* value, 0.2). TSH levels were positively associated with base of support (*P* value, 0.01) and followed an inverted U-shaped curve with tandem (*P* value, 0.002) and velocity (*P* value, 0.02). Clinical and subclinical hypothyroidism were associated with worse global gait than euthyroidism (β, -0.61; 95% confidence interval, -1.03 to -0.18; and β, -0.13; 95% confidence interval, -0.26 to -0.00; respectively). In euthyroid participants, higher thyroid function was associated with worse gait patterns.

Conclusions Both low and high thyroid function are associated with alterations in global gait, tandem, base of support, and velocity.

INTRODUCTION

Gait is an important marker of general health. Disturbances in gait gradually increase with advancing age and affect approximately one third of community-dwelling individuals older than 60 years.[1] Gait impairment has a substantial impact on quality of life and is strongly associated with increased risk of falls, which can in turn cause soft-tissue injuries, fractures, and death.[2,3] Quantitative gait assessment comprises many parameters that can be summarized into seven independent domains, namely rhythm, variability, phases, pace, base of support, tandem, and turning (Figure 1).[4,5] These gait domains reflect distinct functional abilities and their investigation is crucial to identify novel modifiable contributors to gait deterioration.[5]

Thyroid hormones regulate metabolism in most tissues, including neurological and musculoskeletal systems, whose integrated functioning is reflected in gait.[6-8] As gait disturbances, thyroid dysfunction increases in prevalence with advancing age. However, the clinical symptoms of thyroid dysfunction become less pronounced among older adults[9] and this may result in a diagnostic delay and increased risk of systemic complications. Research to date has suggested a possible role of thyroid

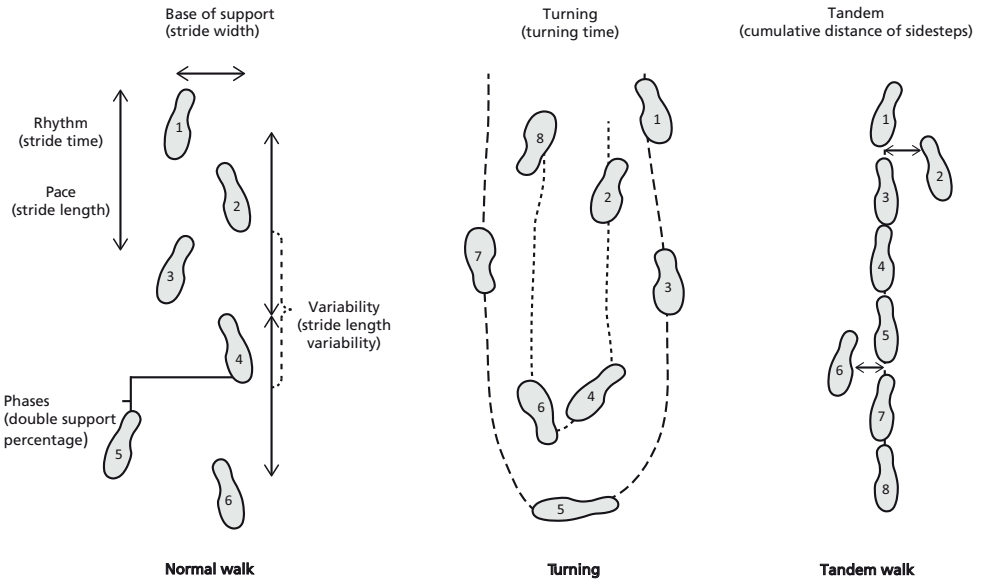


Figure 1. Walking conditions.
The three walking conditions, including five gait domains for normal walk (rhythm, variability, phases, pace, base of support), one for turn (turning) and one for tandem walk (tandem).

dysfunction in gait impairment. Adult mice lacking the thyroid-hormone activating enzyme type 2 deiodinase have shown progressive gait impairment in the late stages of life.[10] In humans, several case series[11,12] and case reports[13-15] have shown a restoration of gait disturbances after treatment of thyroid disease.

Thyroid function in the general population has been linked to gait velocity, which constitutes only one of the parameters in the pace domain.[16,17] However, the link of thyroid function with gait and its spatiotemporal aspects remains unexplored. Therefore, we aimed to investigate the association of thyroid function with global gait and its separate domains, in a large population-based cohort of middle-aged and elderly subjects.

METHODS

Study population

The Rotterdam Study is an ongoing prospective population-based cohort study that investigates chronic diseases in the middle-aged and elderly. The objectives and study design of the Rotterdam Study have been described in detail elsewhere.[18] Rotterdam Study was initiated in 1990, including 7983 participants aged 55 years or older (RS I). In 2000, the cohort was expanded with 3011 participants aged 55 or older (RS II). In 2006, a third cohort of 3932 participants aged 45 years and over was added (RS III). As of now, the Rotterdam Study comprises a total of 14926 participants, who undergo extensive follow-up medical examinations every 3 to 5 years. From 2009 onwards, quantitative gait assessment was included in the study protocol. Between March 2009 and March 2012, 3651 participants of the Rotterdam Study were invited for gait assessment. An overview on the selection of study participants can be found in the flowchart (Supplemental Figure 1).

A total of 2857 subjects had complete information on thyroid function and gait. Of these, we excluded 212 subjects with at least one out of several conditions: (1) dementia diagnosis (n=14); (2) thyroid medication use (n=79); (3) history of thyroid disease (n=192) and (4) previous thyroid surgery (n=33) (Supplemental Figure 1). The remaining 2645 eligible participants were enrolled in the study.

The Medical Ethics Committee of the Erasmus University and the Ministry of Health, Welfare and Sport of the Netherlands have approved the study protocols, implementing the “Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study)”. The methods were performed in accordance with the approved

guidelines. All included participants provided written informed consent in accordance with the Declaration of Helsinki.

Assessment of thyroid function

Thyroid function tests were performed during the third visit of the first cohort (RS I.3), the first visit of the second cohort (RS II.1) and the first visit of the third cohort (RS III.1) using the same method and assay. Concentrations of thyroid-stimulating hormone (TSH), free thyroxine (FT_4) and thyroid peroxidase antibodies (TPOAb) were measured on baseline serum samples stored at -80°C using the electrochemiluminescence immunoassay, ECLIA, Roche. We determined the reference range of serum TSH as 0.40–4.0 mIU/L and serum FT_4 as 11–25 pmol/L (alternatively 0.86–1.94 ng/dL), according to national guidelines and our previous studies.[19,20] Euthyroidism was defined as serum TSH within the reference range. Subclinical hypothyroidism was defined as serum TSH >4.0 mIU/L and FT_4 levels within the reference range. Overt hypothyroidism was defined as serum TSH >4.0 mIU/L and FT_4 levels <11 pmol/L. Subclinical hyperthyroidism was defined as serum TSH <0.40 mIU/L and FT_4 levels within the reference range. Overt hyperthyroidism was defined as serum TSH <0.40 mIU/L and FT_4 levels >25 pmol/L. TPOAb positivity was defined as TPOAb levels above the cutoff of 35 kU/ml, in accordance with the recommendations of the assay manufacturer.[19,20]

Assessment of gait

Quantitative gait assessment was performed during the fifth visit of the first cohort (RS I.5), the third visit of the second cohort (RS II.3) and the first visit of the third cohort (RS III.1). Gait was evaluated using a 5.79 m long walkway (GAITRite Platinum; CIR systems, Sparta, NJ: 4.88-m active area; 120 Hz sampling rate). The reliability and validity of this device have been previously established.[4,21-23] The standardized gait protocol comprises three walking conditions: normal walk, turning, and tandem walk (Figure 1). In the normal walk, participants walked at their usual pace across the walkway. This walk was repeated eight times, of which the first recording was considered a practice walk and excluded from the analyses. In turning, participants walked at their usual pace, turned halfway, and returned to the starting position. In the tandem walk, participants walked heel-to-toe on a line across the walkway. Based on the recorded footfalls, the walkway software calculated thirty gait parameters, including twenty five from the normal walk, two from turning,

and three from the tandem walk. Subsequently, principal component analysis (PCA) was performed to avoid multiple testing and collinearity across the variables. While capturing the largest amount of variance, PCA summarizes gait parameters into seven independent gait domains: rhythm, variability, phases, pace, base of support, tandem, and turning.[5] Rhythm reflects cadence and stride time; variability reflects variations in length and time among strides; phases reflects double support time and double support as a percentage of the gait cycle; pace reflects stride length and gait velocity; base of support reflects stride width and stride width variability; tandem reflects errors in tandem walking; turning reflects turning time and the number of turn steps.[5] When necessary, gait domains were inverted so that lower values represent "worse" gait. Global gait was calculated by averaging gait domains into a standardized Z score.[5] Gait velocity was additionally included in our analysis in order to compare our findings with previous studies investigating the association between thyroid function and gait velocity.[16,17]

Additional measurements

The baseline home interview provided information on medical history, tobacco smoking, alcohol consumption, education level, medication, knee and hip pain or stiffness. Participants were categorized based on their smoking status (current, past and never smokers) and education level (low, intermediate and high). Height and weight were measured during the examinations at the research center. Stroke cases were reviewed and verified by an experienced vascular neurologist using hospital letters, information from practitioners and nursing home physicians. Depressive disorders were evaluated based on the Centre for Epidemiological Studies Depression Scale (CESD) questionnaire. A score above 16 was considered indicative of a depressive disorder.[24] Cerebellar cortical volume and intracranial volume were examined by standardized magnetic resonance imaging (MRI) scanning of the brain.[18]

Statistical analysis

We investigated the association of thyroid parameters (TSH, FT_4, and TPOAb positivity) with global gait and spatiotemporal gait components, by performing ordinary least-squares linear regression. The primary outcome was global gait, while secondary outcomes included gait domains (ie, rhythm, variability, phases, pace, base of support, tandem, and turning), and gait velocity. We fitted restricted cubic splines to allow for potential nonlinearity. Moreover, we evaluated global gait and gait ve-

locity throughout thyroid function categories, with euthyroid subjects as reference group. Next, we examined the association of thyroid function with gait in euthyroid participants. In addition, we performed a sensitivity analysis excluding participants with prevalent stroke (n=66) and Parkinson's disease (n=3).

All analyses were adjusted for potential confounding by age, sex, cohort, smoking status, alcohol intake (Model 1). As thyroid function measurement preceded the gait assessment, we also adjusted for the time interval between measurements. In Model 2, we additionally adjusted for covariates that could be either confounders or mediators, including education level, height, weight, knee pain or stiffness, hip pain or stiffness, prevalent stroke, CESD depression score, cerebellar cortical volume, intracranial volume, TPOAb concentrations. Step count and mean step size can affect the score of tandem walk. Therefore, all models including tandem walk were further adjusted for step count and mean step size.

TSH values were logarithmically transformed, because of its skewed distribution. The assumption of normally distributed residuals was checked and met. All models were tested for effect modification by separately adding product interaction terms of the exposure (TSH or FT_4 or TPOAb) with covariates of the multivariable model, but none of the interaction terms were significant. Multiple imputations were performed for covariates with missing data (less than 4.6% for all covariates). A *P* value (two-tailed) <0.05 was considered statistically significant. Statistical analyses were conducted using R statistical software (rms package, R project, Institute for Statistics and Mathematics, R Core Team, version 3.2.2) and IBM SPSS version 21 (IBM Corp).

RESULTS

We included a total of 2645 eligible participants with data available on thyroid function and gait, without known thyroid disease or dementia (Supplemental Figure 1). The baseline characteristics of the study population are shown in Table 1. The mean age was 59.6 years and 52.6% were females (Table 1).

Thyroid function and global gait

Our results did not change after primary and additional adjustments for potential confounders; therefore, we further report only the most adjusted model (Model 2). TSH concentrations within the full range followed an inverted U-shaped curve with global gait (*P* value, <0.001; Figure 2a). However, there was no association of

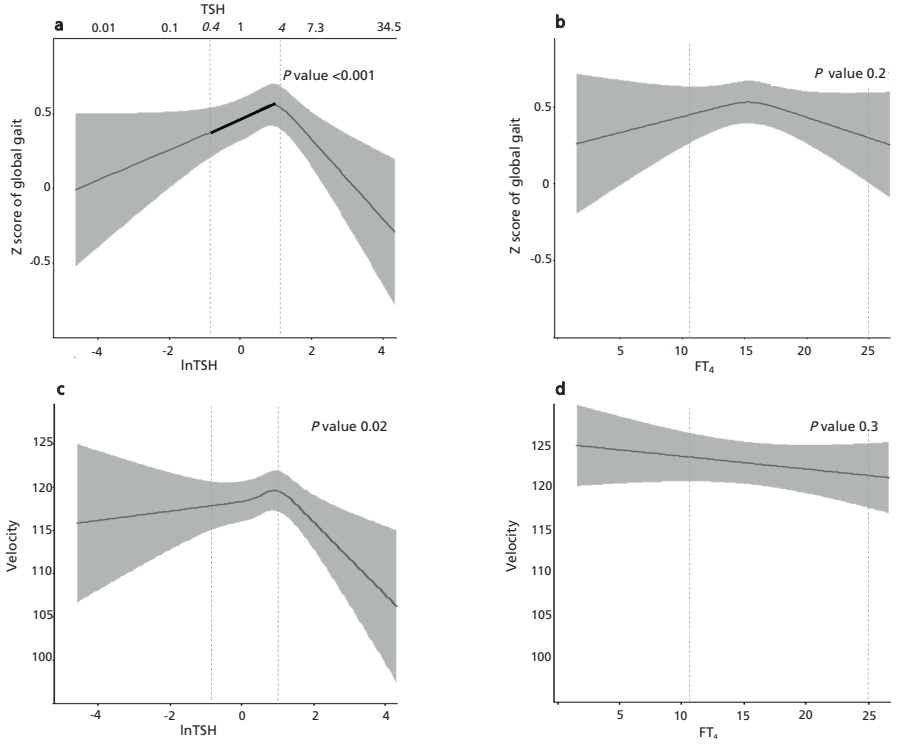
Table 1. Baseline characteristics of 2645 participants*

Age, years	59.6 (6.6)
Women, n (%)	1392 (52.6)
Smoking, n (%)	
current	561 (21.2)
past	1242 (47.0)
never	842 (31.8)
Alcohol intake >14 drinks/week, n (%)	565 (21.4)
Education level, n (%)	
low	195 (7.4)
intermediate	1821 (68.8)
high	629 (23.7)
Height, cm	170.0 (9.2)
Weight, kg	78.4 (14.1)
Knee pain or stiffness, n (%)	693 (26.2)
Hip pain or stiffness, n (%)	401 (15.2)
Past stroke, n (%)	66 (2.5)
CESD depressive symptoms, n (%)	298 (11.3)
Cerebellar cortical volume, ml	99.3 (10.6)
Intracranial volume, ml	1479.6 (159.6)
TSH, mIU/L, median (IQR)	1.9 (1.3-2.8)
FT_4, pmol/L	15.5 (2.1)
TPOAb positive, n (%)	312 (11.8)

*Data are presented as mean (standard deviation), unless otherwise specified. Abbreviations: CESD, Centre for Epidemiological Studies Depression Scale; TSH, thyroid-stimulating hormone; IQR, interquartile range; FT_4, free thyroxine; TPOAb, thyroid peroxidase antibodies (cutoff 35 kU/ml).

FT_4 concentrations with global gait (*P* value, 0.2; Figure 2b). When we restricted the analysis to euthyroid participants, higher TSH concentrations were associated with a better global gait (β, 0.08; 95% confidence interval [95% CI], 0.02 to 0.13 per 1 unit logTSH). Moreover, there was a borderline statistically significant association between FT_4 levels within the normal range and global gait (β, -0.05; 95% CI, -0.10 to 0.00 per 1 pmol/L FT_4; Figure 2 and Supplemental Table 1). Clinical and subclinical hypothyroidism were associated with a worse global gait than euthyroidism (β, -0.61; 95% CI, -1.03 to -0.18 and β, -0.13; CI, -0.26 to -0.00, respectively; Figure 3a). No association was observed between TPOAb and global gait in the main analysis or after restricting to euthyroid participants (Supplemental Table 2). Results remained similar after excluding participants with prevalent stroke and Parkinson's disease (Supplemental Figure 2).

Figure 2. Association of thyroid function with global gait and velocity.

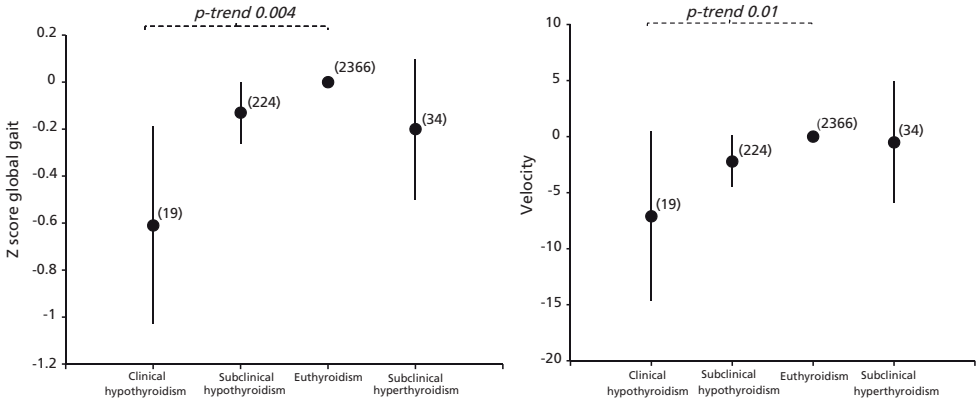


Adjusted for age, sex, cohort, smoking, alcohol intake, education level, height, weight, time interval between thyroid function measurement and gait assessment, knee pain or stiffness, hip pain or stiffness, prevalent stroke, CESD depression score, cerebellar cortical volume, intracranial volume, and thyroid peroxidase antibodies. We utilized linear regression models with restricted cubic splines. Predicted means of Z score global gait and velocity (black lines) with 95% CI (gray areas) are plotted against TSH/FT_4 concentrations. Dashed lines indicate the limits of TSH or FT_4 reference ranges. A higher value of global gait represents better gait.

Thyroid function, gait domains and gait velocity

TSH levels were positively linearly associated with base of support (*P* value, 0.01; Figure 4e) and followed an inverted U-shaped curve with respect to tandem (*P* value, 0.002; Figure 4f) and gait velocity (*P* value, 0.02; Figure 2c). In euthyroid participants, higher TSH levels were associated with higher base of support (β, 0.07; 95% CI, 0.01 to 0.14) and tandem (β, 0.06; 95% CI, 0.01 to 0.12), whereas higher FT_4 levels were associated with lower gait velocity (β, -0.96; 95% CI, -1.85 to -0.07; Supplemental Table 1). Clinical and subclinical hypothyroidism were associated with lower gait velocity than euthyroidism, with borderline statistical significance (β, -7.11; 95% CI, -14.69 to 0.49 and β, -2.22; 95% CI,- 4.50 to 0.05, respectively). Gait velocity decreased gradually from euthyroidism to clinical hypothyroidism (*P* for trend, 0.01) (Figure 3b).

Figure 3. Association of thyroid status categories with global gait and velocity.



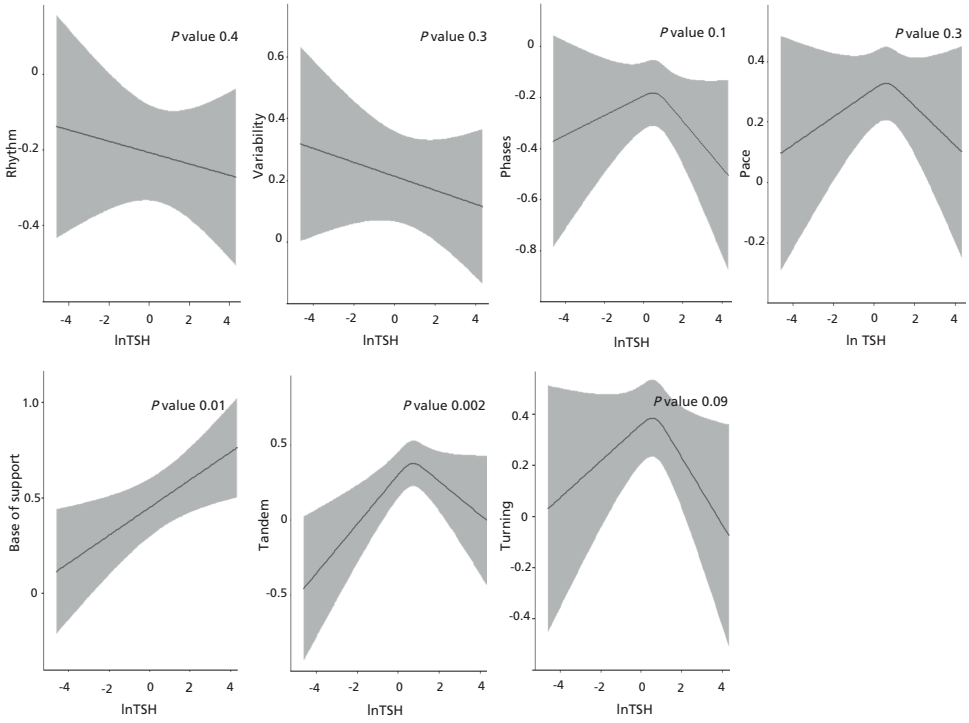
Adjusted for age, sex, cohort, smoking, alcohol intake, education level, height, weight, time interval between thyroid function measurement and gait assessment, knee pain or stiffness, hip pain or stiffness, prevalent stroke, CESD depression score, cerebellar cortical volume, intracranial volume, and thyroid peroxidase antibodies. Differences in Z score of global gait and velocity are plotted against thyroid status categories, with euthyroid subjects as reference. Euthyroidism was defined as TSH (thyroid-stimulating hormone) within reference range (0.4 to 4.0 mIU/l); clinical hypothyroidism as TSH >4.0 mU/L and FT_4 (free thyroxine) <11 pmol/L; subclinical hypothyroidism as TSH >4.0 mU/L and FT_4 11 to 25 pmol/L; clinical hyperthyroidism as TSH <0.4 mU/L and FT_4 >25 pmol/L; subclinical hyperthyroidism as TSH < 0.4 mU/L and FT_4 11 to 25 pmol/L. None of the participants had clinical hyperthyroidism. Error bars represent the 95% confidence intervals around the standardized β (black dots). Within brackets: Total number. A higher value of global gait represents better gait.

DISCUSSION

In a large cohort of middle-aged and elderly subjects, we reported an inverted U-shaped association between TSH concentrations and global gait, indicating that both low and high thyroid function are associated with worse gait. TSH levels were positively associated with base of support and followed an inverted U-shaped curve with tandem and gait velocity. In euthyroid subjects, higher thyroid function was associated with worse gait patterns.

The association between thyroid function and gait could be explained by different pathophysiological mechanisms, particularly involving the neurological and musculoskeletal systems. Low and high thyroid function may increase the risk of stroke via unfavorable cardiovascular risk profile and atrial fibrillation, respectively.[25,26] Low thyroid function can additionally induce immune-mediated cerebellar degeneration.[14] Furthermore, low and high thyroid function can lead to a dysregulation of the neurotransmission systems and subsequent depressive symptoms.[27] Low and high thyroid function may also contribute to myopathy and fractures, by affecting muscle mass and bone mineral density.[28,29] In turn, stroke, cerebellar degeneration,

Figure 4. Association of TSH with the seven gait domains.



Adjusted for age, sex, cohort, smoking, alcohol intake, education level, height, weight, time interval between thyroid function measurement and gait assessment, knee pain or stiffness, hip pain or stiffness, prevalent stroke, CESD depression score, cerebellar cortical volume, intracranial volume, and thyroid peroxidase antibodies. The model including tandem walk was additionally adjusted for step count and mean step size. Point estimates are reported as predicted means (black lines) of gait domains with 95% CI (gray areas). A higher value of gait domains represents better gait.

depression, myopathy and fractures are all implicated in gait deterioration.[14,25-29] In our study, adjustments for stroke, cerebellar cortical volume, TPOAb, CESD depression score, hip and knee pain or stiffness (proxy for musculoskeletal dysfunction) did not change the results, suggesting that the association between thyroid function and gait patterns is independent of these factors. Alternative underlying pathways can explain the association. The most plausible may be peripheral neuropathy, given that thyroid dysfunction has been commonly associated with axonal degeneration and nerve conduction abnormalities.[28,30,31] Both hypothyroid and hyperthyroid patients usually experience symmetric distal sensory disturbances that can resolve after treatment of thyroid dysfunction.[28,32] Also, genetic disorders affecting thyroid hormone transport and metabolism may play a role in gait impairment.[33] However, the exact mechanisms through which thyroid function could affect the gait patterns

remain unexplored and further studies should be directed towards unravelling the underlying pathophysiology.

Although gait is a multidimensional concept, gait assessment in prior comparable studies has been limited to the measurement of gait velocity.[16,17] A relatively small study (n=602) reported an association of high-normal FT_4 levels with slower walk.[17] A second study reported a faster walk in individuals with mildly elevated TSH levels (4.5-7.0 mIU/L) compared with euthyroid individuals.[16] Our conclusions are in line with the results of the first study, but do not support those of the second study. Most likely, the discrepancy between our results and those of the second study may be attributable to differences in TSH reference ranges and thyroid status definitions. In the second study, participants with TSH levels between 4.5 and 7.0 mIU/L were considered to have mild subclinical hypothyroidism, though they lacked FT_4 measurements. Instead, we used both TSH and FT_4 measurements to define the thyroid status of our participants. Therefore, our conclusions may add valuable information to the ongoing debate on the effects of untreated or undetected subclinical hypothyroidism. Most importantly, our large population-based cohort study extends the previous literature by addressing for the first time the association of thyroid function with global gait and gait domains. Our results indicate the importance of comprehensive gait evaluation, as we observe a stronger association of thyroid status with global gait than with gait velocity.

We were able to identify tandem, base of support and gait velocity as spatiotemporal gait aspects related to thyroid function. Likewise, past case reports have described hypothyroid patients with a "wide-based gait" and tandem walking errors on neurological examination.[12-15] In addition, adult mice lacking type 2 deiodinase walked slower and with wider base of support than the wild-type mice.[10] Our results confirm these findings in the setting of a general population cohort study. Of note, the identification of thyroid-related gait domains may provide valuable hints on the pathways linking thyroid function to gait. Tandem, base of support, and gait velocity have been associated with distinct brain structures (ie, prefrontal regions, parietal cortex, pallidum, putamen, and cerebellum), executive functioning and balance, that might be specific targets of thyroid hormone action.[4,15,34-38]

A limitation of our study is its cross-sectional design, which does not enable us to draw conclusions on causality. Though it is more likely that thyroid function affects gait than vice-versa, one could also hypothesize that health problems underlying gait abnormalities may alter thyroid parameters in the setting of non-thyroidal

illness syndrome (NTIS). This condition is characterized by low thyroid hormones and normal TSH levels.[39] Instead, we reported a nonlinear association between TSH levels and global gait. Also, NTIS is typical in critically ill patients, whereas the Rotterdam Study consists of community-dwelling adults.[39] Therefore, NTIS is unlikely to be the explanation of our findings. Furthermore, turning and tandem walk lacked repeated measurements, which would have reduced the intra-individual variability. However, we did perform up to eight consecutive recordings of the normal walk, and used a well validated instrument for an objective gait evaluation in three walking conditions. Also, the Rotterdam Study does not have data available on serum triiodothyronine levels, which is a limitation for most population-based studies. However, TSH and FT_4 concentrations are considered as the most relevant measurements of thyroid function in clinical practice. Moreover, Rotterdam Study includes predominantly Caucasians over 45 years old, which limits the generalizability of our findings to other populations. Lastly, the possibility of residual confounding cannot be excluded, even though we controlled for multiple potential confounders.

Conclusions

Both low and high thyroid function are associated with worse gait patterns. There is an inverted U-shaped association of TSH levels with global gait, tandem, and gait velocity, as well as a positive association of TSH levels with base of support. Subjects with clinical and subclinical hypothyroidism have worse gait patterns than euthyroid individuals. These conclusions might have future implications regarding the prevention and treatment of thyroid and gait disorders. Further studies are needed to confirm our findings, determine the underlying mechanisms linking thyroid function to gait patterns and subsequently investigate the possible motor benefits of thyroid treatment.

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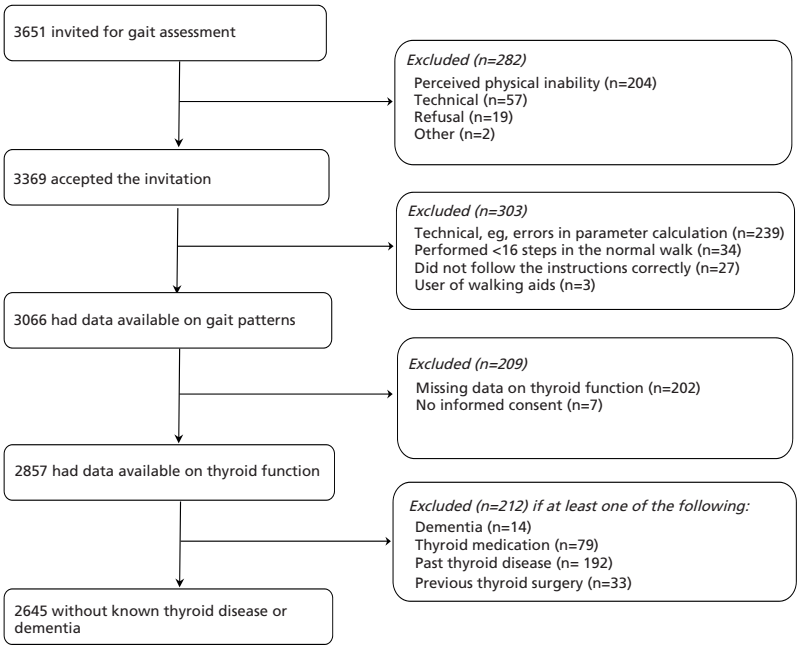
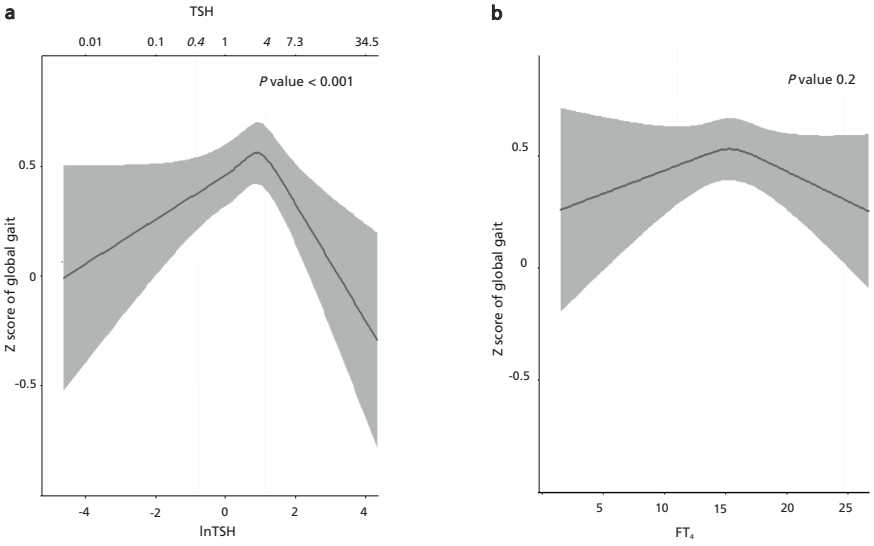
SUPPLEMENTAL MATERIAL

Supplemental Figure 1. Flow chart for the selection of study participants.



Supplemental Figure 2. Association of thyroid function with global gait, after excluding participants with prevalent stroke and Parkinson's disease.



Supplemental Table 1. Association of thyroid function with global gait, gait domains and gait velocity in euthyroid participants*

	TSH β (95% CI)	FT_4 β (95% CI)
Global gait	**0.08 (0.02; 0.13)**	-0.05 (-0.10; 0.00)
Rhythm	0.00 (-0.06; 0.06)	-0.02 (-0.07; 0.03)
Variability	0.02 (-0.04; 0.08)	-0.01 (-0.06; 0.04)
Phases	0.02 (-0.03; 0.08)	-0.05 (-0.10; 0.00)
Pace	0.05 (0.00; 0.10)	-0.02 (-0.07; 0.02)
Base of support	**0.07 (0.01; 0.14)**	0.01 (-0.04; 0.06)
Tandem†	**0.06 (0.01; 0.12)**	-0.03 (-0.08; 0.02)
Turning	-0.02 (-0.08; 0.04)	-0.01 (-0.06; 0.05)
Velocity	0.87 (-0.12; 1.87)	**-0.96 (-1.85;-0.07)**

A higher value of gait represents better gait. Analyses are adjusted for age, sex, cohort, smoking, alcohol intake, education level, height, weight, time interval between thyroid function measurement and gait assessment, knee pain or stiffness, hip pain or stiffness, prevalent stroke, CESD depression score, cerebellar cortical volume, intracranial volume, and thyroid peroxidase antibodies. *Euthyroidism was defined as TSH within the reference range (0.4 to 4.0 mIU/L). †Additionally adjusted for step count and step size within tandem walk. Abbreviations: TSH, thyroid-stimulating hormone, is per one unit increase of log transformed TSH (mIU/L); FT_4, free thyroxine, is per one unit increase of FT_4 (pmol/L); β, regression coefficient; CI, confidence interval.

Supplemental Table 2. Association of TPOAb positivity* with global gait

	β (95% CI)
All participants	-0.05 (-0.16; 0.06)
Euthyroid participants†	-0.06 (-0.19; 0.06)

A higher value of global gait represents better gait. Analyses are adjusted for age, sex, cohort, smoking, alcohol intake, education level, height, weight, time interval between thyroid function measurement and gait assessment, knee pain or stiffness, hip pain or stiffness, prevalent stroke, CESD depression score, cerebellar cortical volume, intracranial volume, and lnTSH. *TPOAb >35 kU/ml were regarded as positive. †Euthyroidism was defined as TSH within the reference range (0.4 to 4.0 mIU/L). Abbreviations: TPOAb, thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone.

CHAPTER 3.3

DIFFERENCES IN TOTAL LIFE EXPECTANCY AND LIFE EXPECTANCY WITH AND WITHOUT CARDIOVASCULAR DISEASE WITHIN THE REFERENCE RANGE OF THYROID FUNCTION

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ABSTRACT

Background Variations in thyroid function within reference ranges are associated with an increased risk of cardiovascular disease (CVD) and mortality. However, the impact of thyroid function on life expectancy and the number of years lived with and without CVD remains unknown. In a large population-based prospective cohort study, we therefore aimed to investigate the association of thyroid function with total life expectancy and life expectancy with and without CVD among euthyroid individuals.

Methods We included participants of the Rotterdam Study without known thyroid disease and with thyroid-stimulating hormone (TSH) and free thyroxine (FT_4) levels within the reference ranges. Multistate life tables were used to calculate total life expectancy and life expectancy with and without CVD among TSH and FT_4 tertiles. Life expectancy estimates in men and women aged 50 years and older were obtained using prevalence, incidence rates and hazard ratios for 3 transitions (healthy to CVD, healthy to death, and CVD to death), adjusting for sociodemographic and cardiovascular risk factors.

Results The mean (standard deviation) age of 7785 participants was 64.7 (9.8) years and 52.5% were women. Over a median follow-up of 8.1 (interquartile range 2.7 to 9.9) years, we observed 789 incident CVD events and 1357 deaths. Compared with those in the lowest tertile, men and women in the highest TSH tertile lived 2.0 (95% confidence interval [95% CI], 1.0 to 2.8) and 1.4 (95% CI, 0.2 to 2.4) years longer, respectively; of which 1.5 (95% CI, 0.2 to 2.6) and 0.9 (95% CI, -0.2 to 2.0) years longer without CVD. Compared with those in the lowest tertile, the difference in life expectancy for men and women in the highest FT_4 tertile was -3.2 (95% CI,-5.0 to -1.4) and -3.5 (95% CI, -5.6; -1.5), respectively; of which -3.1 (95% CI, -4.9 to -1.4) and -2.5 (95% CI, -4.4 to -0.7) years without CVD.

Conclusions At the age of 50 years, participants with low-normal thyroid function live up to 3.5 years longer overall and up to 3.1 years longer without CVD than participants with high-normal thyroid function. These findings provide supporting evidence for a reevaluation of the current reference ranges of thyroid function and can help inform preventive and clinical care.

INTRODUCTION

Thyroid dysfunction is one of the most common endocrine disorders.[1] Clinical thyroid dysfunction is characterized by thyroid-stimulating hormone (TSH) and free thyroxine (FT_4) levels outside the reference ranges, whereas subclinical thyroid dysfunction is characterized by TSH levels outside the reference range combined with FT_4 levels within the reference range. At present, the reference ranges for TSH and FT_4 levels are statistically determined on the basis of the 2.5th and 97.5th percentiles of an apparently healthy population. This arbitrary approach, however, has been recently challenged by studies suggesting that the current reference ranges of thyroid function may need to be reevaluated by additionally taking into account the risk of clinical outcomes.[2-5] In view of the ongoing debate on redefining the reference ranges of TSH and FT_4 levels, there is a need for novel insights about the qualitative and quantitative impact of thyroid function on an individual's life and health.

The cardiovascular system represents a major target of thyroid hormone action.[6] Both clinical and subclinical thyroid dysfunction have been associated with an increased risk of coronary heart disease,[7,8] heart failure[9] and mortality.[7,8,10,11] These deleterious effects of thyroid dysfunction might also be extended to the euthyroid range. Many studies conducted in middle-aged and elderly euthyroid individuals have reported an increased risk of cardiovascular disease (CVD) and mortality with lower TSH and/or higher FT_4 levels.[2-5,12-16] Other studies do not find an association,[17-19] probably due to the relatively small proportion of events,[17,18] insufficient sample sizes[19] or short term follow-up.[17] However, it remains unclear whether there are meaningful differences in the remaining years of life lived with and without CVD within the reference range of thyroid function. Therefore, in a large population of euthyroid subjects, we aimed to investigate the association of thyroid function with total life expectancy (LE) and LE with and without CVD.

METHODS

Study population

This study was embedded within the Rotterdam Study, a large prospective population-based cohort study. The objectives and design have been described in detail previously.[20] The Rotterdam Study was initiated in 1989, including 7983 participants aged 55 years or older. In 2000, the study was extended with a second cohort of 3011 subjects. In 2006, a third cohort of 3932 subjects aged 45 years or older was added.

Study participants undergo extensive follow-up medical examinations every 3 to 5 years. Baseline measurements for our study were performed during the third visit of the first cohort (1997-1999, n=4797) and the first visit of the second (2000-2001, n=3011) and third (2006-2008, n=3932) cohorts of the Rotterdam Study. The original cohort during these three visits included a total of 11740 participants, of which 10050 had available blood measurements. Thyroid function measurements were performed in a random sample of 9702 participants. Of these, we excluded 16 participants without complete follow-up data, 1346 with TSH or FT_4 outside the normal reference ranges and 555 with past thyroid disease or taking thyroid medications. The remaining 7785 participants were eligible for the analysis (Supplemental Figure 1). Follow-up started at the date of thyroid function assessment.

The protocols of the Rotterdam Study have been approved by the Medical Ethics Committee of the Erasmus University and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the Population Study Act Rotterdam Study. In accordance with the Declaration of Helsinki, all included participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

Assessment of thyroid function

Thyroid function was assessed during the third visit of the first cohort (RS I.3) and the first visit of the second (RS II.1) and third (RS III.1) cohorts using the same method and assay. Measurements of TSH and FT_4 were performed in baseline serum samples stored at -80°C using the electrochemiluminescence immunoassay ECLIA Roche. The reference ranges of TSH (0.40–4.0 mIU/L) and FT_4 (0.86–1.94 ng/dL, alternatively 11–25 pmol/L) were determined based on national guidelines and our previous studies.[21,22]

Assessment of CVD and mortality

Outcome measures were incident nonfatal CVD, fatal CVD and overall mortality. CVD was defined as presence of coronary heart disease, stroke or heart failure. Coronary heart disease was defined as coronary revascularization (as a proxy for significant coronary artery disease), fatal or nonfatal myocardial infarction or fatal coronary heart disease.[23] Based on the World Health Organization criteria, stroke was defined as a syndrome of rapidly developing symptoms, with an apparent vascular cause of focal or global cerebral dysfunction lasting 24 hours or longer or leading to death.[20,24] Based on the European Society of Cardiology criteria, heart

failure was defined as the presence of typical symptoms and signs (ie, breathlessness at rest or during exertion, ankle edema, and pulmonary crepitations), confirmed by the objective evidence of cardiac dysfunction (ie, chest X-ray, echocardiography) or a positive response to the initiated treatment.[25] Prevalent CVD was assessed at baseline through interview and medical records. After enrollment, participants were continuously monitored for incident CVD through linkage of the study database with files from general practitioners and hospital records.

Information on mortality was obtained from municipality records, general practitioners, and reports of medical specialists. The underlying cause of death was ascertained independently by 2 research physicians and subsequently validated by a medical specialist.[23]

Additional measurements

The baseline home interview provided information on medical history, medication use, tobacco smoking, alcohol consumption, education level and marital status.[20] Smoking habits were categorized as current, former and never smoking. Education level was divided into four categories: elementary, lower secondary, higher secondary and tertiary education, in accordance with the standard international classification of education.[26] Marital status was categorized as single, married, widowed and divorced/separated. Serum glucose and lipid levels were measured by an automated enzymatic procedure (Mannheim System). Anthropometric measurements were performed in the research center by trained medical staff. Body mass index was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured in the sitting position on the right arm and calculated as the mean of two measurements using a random-zero sphygmomanometer. Diabetes mellitus was defined as fasting serum glucose level of 7 mmol/L or more, non-fasting plasma glucose level of 11.1 mmol/L or more (when fasting samples were absent) or the use of antidiabetic medications.[20]

Statistical analysis

Total LE and the number of years lived with and without CVD were calculated among tertiles of TSH and FT_4, by using multistate lifetables. Differences in LE were evaluated using the lowest tertile as reference. Multistate life tables combined information from participants in 3 possible health states, namely "free of CVD", "CVD", and "death". Possible transitions of participants were: (1) from free of CVD to CVD (incident CVD); (2) from free of CVD to death (mortality among those with-

out CVD); (3) from CVD to death (mortality among those with CVD). Backflows were not allowed and only the first event into a state was considered.[27] To calculate LE, we followed a similar approach to previous studies.[28,29]

Due to the known gender differences in LE, analyses were performed separately among men and women. We first calculated the prevalence of TSH tertiles among participants with and without CVD, categorized in 10-year age groups. In each transition, we calculated age-specific incidence rates. Next, we applied Poisson regression with Gompertz distribution to compute hazard ratios (HRs) of the association between TSH tertiles and incident CVD or mortality. The confidence intervals of LE estimates were calculated using Monte Carlo method with 10000 bootstrap simulations.[30] Moreover, we repeated the analyses for the FT_4 tertiles.

Analyses were adjusted for potential confounders, which were selected on the basis of biological plausibility and previous literature. Model 1 was adjusted for age and cohort. Model 2 was adjusted for age, cohort, smoking, alcohol intake, education level, marital status, diabetes mellitus, body mass index, systolic blood pressure, total cholesterol, triglycerides, and use of antihypertensive and lipid-lowering medications.

Multiple imputations were performed in case of missing covariates (<5% for all covariates). Statistical analyses were conducted using IBM SPSS version 21 (IBM Corp), STATA version 13 for Windows (StataCorp, College Station, Texas) and @RISK software (Palisade).

Sensitivity analysis

Several sensitivity analyses were performed: (1) To account for potential reverse causation, we excluded CVD events (n=179) or deaths (n=293) that occurred during the first 2 years of follow-up; (2) We excluded participants using thyroid function-altering medications (ie, amiodarone and corticosteroids) (n=137); (3) To exclude any potential bias caused by presence of cancer at baseline, we additionally adjusted our analyses for prevalent cancer at baseline; (4) To detect a potential influence of follow-up duration on our results, we performed the analyses restricting the length of follow-up to 8 years (median follow-up time).

To additionally explore the association between thyroid status categories (ie, hypothyroidism, euthyroidism, hyperthyroidism) and LE with and without CVD, we extended the study population, including participants of the Rotterdam Study with data available on thyroid function and CVD, without past thyroid disease and not

using thyroid function-altering medications (ie, thyroid medications, amiodarone or corticosteroids). Participants were categorized on the basis of their thyroid status. Euthyroidism was defined as serum TSH levels within the reference range. Hypothyroidism (clinical and subclinical combined) was defined as high TSH combined with low or normal FT_4. Hyperthyroidism (clinical and subclinical combined) was defined as low TSH combined with high or normal FT_4. Total LE and LE with and without CVD were calculated in men and women, among thyroid status categories, by using multistate lifetables. Differences in LE were evaluated using the euthyroid category as reference.

RESULTS

Baseline characteristics of 7785 eligible participants are presented in Table 1. The mean (standard deviation) age of participants was 64.7 (9.8) years and 52.5% were women. Over a median follow-up time of 8.1 (interquartile range, 2.7 to 9.9) years, 789 incident CVD events and 1357 deaths occurred. Both models yielded similar estimates, therefore we further report the results of the most adjusted model (Model 2).

Association of thyroid function within the reference range with the risk of CVD and death

The association of TSH tertiles with the risk of incident CVD was not statistically significant (highest versus lowest TSH tertile: HR, 0.93; 95% CI, 0.79 to 1.11) (Table 2). Compared with the lowest tertile, the highest TSH tertile was associated with a lower risk of mortality among participants without CVD (HR, 0.76; 95% CI, 0.64 to 0.91) and with CVD (HR, 0.82; 95% CI, 0.67 to 1.01) (Table 2).

The highest FT_4 tertile was associated with a 1.32 times higher risk of incident CVD than the lowest tertile (95% CI, 1.10 to 1.58) (Table 2). Compared with the lowest tertile, the highest FT_4 tertile was also associated with a 1.64 times higher risk of mortality among participants with CVD (95% CI, 1.32 to 2.02) and a 1.45 times higher risk of mortality among participants without CVD (95% CI, 1.21 to 1.73) (Table 2).

Results for TSH and FT_4 analyses did not change substantially after the events that occurred during the first 2 years of follow-up were excluded (Supplemental Table 1). Also, results remained similar after excluding users of thyroid function-altering medications and additionally adjusting for the presence of prevalent cancer at baseline (Supplemental Table 2).

Table 1. Baseline characteristics of 7785 participants*

	Men	Women
Number	3699	4086
Age, years	64.3 (9.3)	65.0 (10.2)
Smoking, n (%)		
current	906 (24.5)	828 (20.3)
former	2180 (58.9)	1553 (38.0)
never	613 (16.6)	1705 (41.7)
Education, n (%)		
Elementary	342 (9.2)	605 (14.8)
Lower secondary	1051 (28.4)	2060 (50.4)
Higher secondary	1354 (36.6)	924 (22.6)
Tertiary	952 (25.7)	497 (12.2)
Marital status, n (%)		
Single	115 (3.1)	252 (6.2)
Married	3155 (85.3)	2515 (61.6)
Widowed	227 (6.1)	897 (22.0)
Divorced/Separated	202 (5.5)	422 (10.3)
Diabetes mellitus, n (%)	497 (13.4)	464 (8.9)
BMI, kg/m^2	27.0 (3.5)	27.3 (4.6)
Systolic blood pressure, mm Hg	141.0 (20.2)	137.9 (21.5)
Use of antihypertensive medications, n (%)	816 (22.1)	942 (23.1)
Total cholesterol, mmol/l	5.4 (0.9)	5.9 (1.0)
Triglycerides, mmol/l	1.6 (0.9)	1.5 (0.7)
Use of lipid-lowering medications, n (%)	666 (18)	583 (14.3)
Prevalent cancer, n (%)	201 (5.4)	250 (6.1)
TSH, mIU/L, median (IQR)	1.8 (1.2-2.4)	1.9 (1.3-2.6)
FT_4, pmol/L	15.9 (2.0)	15.6 (1.9)

*Data are presented as mean (standard deviation), unless otherwise specified. Abbreviations: BMI, body-mass index; TSH, thyroid-stimulating hormone; IQR, interquartile range; FT_4, free thyroxine.

Association of thyroid function within the reference range with total LE and LE with and without CVD

Total LE increased significantly from the lowest to the middle TSH tertile and did not change substantially from the middle to the highest TSH tertile (Figure 1). Compared with those in the lowest tertile, men in the highest TSH tertile lived 2.0 (95% CI, 1.0 to 2.8) years longer overall, of which, 1.5 (95% CI, 0.2 to 2.6) years longer without CVD and 0.5 (95% CI, -0.5 to 1.4) years longer with CVD (Table 3). Compared with those in the lowest tertile, women in the highest TSH tertile lived 1.4 (95% CI, 0.2 to 2.4) years longer overall, of which, 0.9 (95% CI, -0.2 to 2.0) years longer without CVD and 0.5 (95% CI, -0.5 to 1.2) years longer with CVD (Table 3).

Table 2. HRs for incident CVD and death among TSH and FT_4 tertiles

			TSH		FT_4	
Transition	**Cases/PY**	**TSH/FT_4 tertiles**	**HR (95% CI) Model 1**	**HR (95% CI) Model 2**	**HR (95% CI) Model 1**	**HR (95% CI) Model 2**
Incident CVD	789/38417	Tertile 1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
		Tertile 2	0.85 (0.72; 1.01)	0.86 (0.72; 1.01)	1.16 (0.97; 1.38)	1.15 (0.97; 1.38)
		Tertile 3	0.93 (0.79; 1.10)	0.93 (0.79; 1.11)	**1.33 (1.11; 1.58)**	**1.32 (1.10; 1.58)**
Mortality among those without CVD	801/41130	Tertile 1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
		Tertile 2	**0.74 (0.62; 0.87)**	**0.75 (0.64; 0.89)**	**1.20 (1.00; 1.44)**	1.19 (0.99; 1.42)
		Tertile 3	**0.72 (0.61; 0.86)**	**0.76 (0.64; 0.91)**	**1.50 (1.26; 1.79)**	**1.45 (1.21; 1.73)**
Mortality among those with CVD	556/8718	Tertile 1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
		Tertile 2	0.95 (0.77; 1.15)	0.92 (0.75; 1.13)	1.24 (0.99; 1.55)	**1.27 (1.01; 1.60)**
		Tertile 3	**0.81 (0.62; 0.91)**	0.82 (0.67; 1.01)	**1.59 (1.29; 1.95)**	**1.64 (1.32; 2.02)**

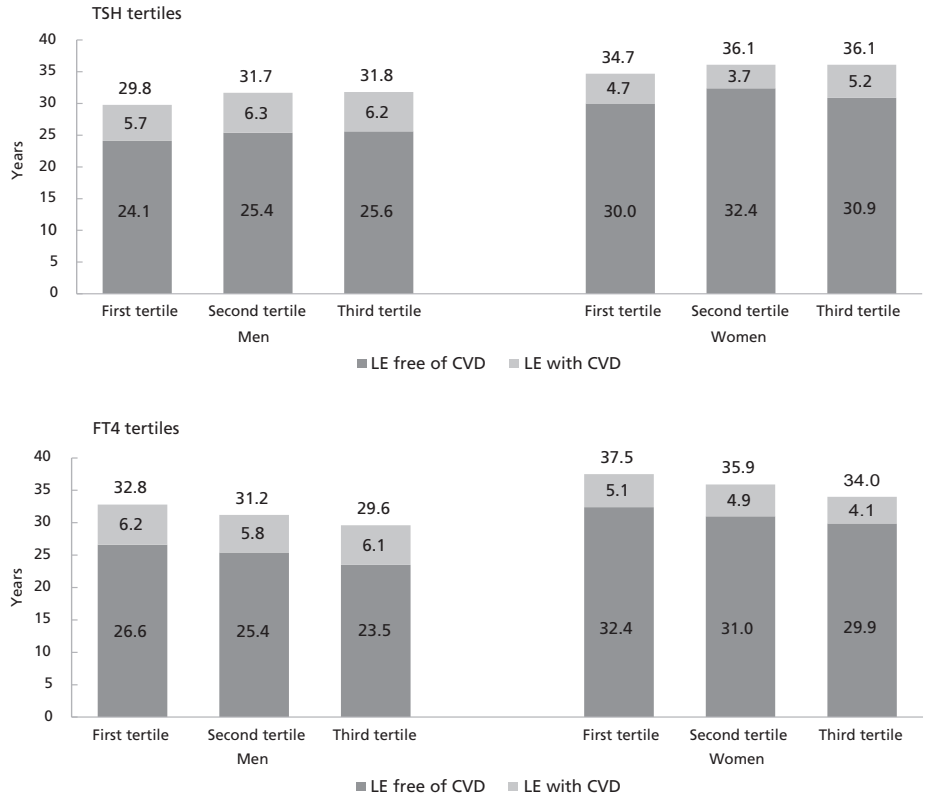
Model 1: age, sex, and cohort. Model 2: Model 1, smoking, alcohol intake, education level, marital status, diabetes mellitus, body mass index, systolic blood pressure, total cholesterol, triglycerides, use of antihypertensive medications, and use of lipid-lowering medications. Abbreviations: HR, hazard ratio; TSH, thyroid-stimulating hormone; FT_4, free thyroxine; PY, person-years; CI, confidence interval; CVD, cardiovascular disease.

Total LE decreased progressively with increasing FT_4 tertiles (Figure 1). Compared with those in the lowest tertile, the differences in LE for men in the highest FT_4 tertile was -3.2 (95% CI, -5.0; -1.4) years overall; of which -3.1 (95% CI, -4.9 to -1.4) years without CVD and -0.1 (95% CI, -1.7 to 1.6) years with CVD (Table 3). Compared with those in the lowest tertile, the difference in LE for women in the highest FT_4 tertile was -3.5 (95% CI, -5.6 to -1.5) years fewer overall, of which -2.5 (95% CI, -4.4 to -0.7) years without CVD and -1.0 (95% CI, -2.4 to 0.4) years with CVD (Table 3). Results were consistent over the length of follow-up of 8 years (Supplemental Table 3).

Association of thyroid status with total LE and LE with and without CVD

Compared with their euthyroid counterparts, hypothyroid men and women lived 0.3 (95% CI, -1.7 to 1.9) and 1.1 (95% CI, -0.4 to 2.3) years longer, respectively (Supplemental Table 4). The difference in LE for hyperthyroid men was -1.4 (95% CI, -4.4 to 2.0) years compared with euthyroid men. However, these results were not statistically significant. The difference in LE for hyperthyroid women was 2.3 (95% CI, 0.2 to 4.4) years without CVD and -1.9 (95% CI, -3.1 to -0.4) years with CVD, compared with euthyroid women (Supplemental Table 4).

Figure 1. Life expectancy with and without CVD at age 50 years among TSH and FT_4 tertiles, in men and women.



Abbreviations: LE, life expectancy; CVD, cardiovascular disease; TSH, thyroid-stimulating hormone; FT_4, free thyroxine.

DISCUSSION

In a large prospective population-based cohort study among middle-aged and elderly participants, we investigated differences in LE with and without CVD within the reference range of thyroid function. Participants with low-normal thyroid function lived up to 3.5 years longer overall and up to 3.1 years longer without CVD than participants with high-normal thyroid function. Total LE in euthyroid participants increased from the lowest to the middle TSH tertile but did not change substantially from the middle to the highest TSH tertile. Total LE in euthyroid participants decreased progressively with increasing FT_4 tertiles. Overall, there were no meaningful sex differences throughout TSH and FT_4 tertiles.

LE without CVD is the resultant of 2 components: risk of incident CVD (transition 1) and risk of mortality among participants without CVD (transition 2). Compared

Table 3. LE at age 50 years among TSH and FT_4 tertiles, in men and women*

TSH/FT_4 tertiles	Total LE	Differences in total LE†	LE free of CVD	Differences in LE free of CVD†	LE with CVD	Differences in LE with CVD†
TSH tertiles						
Men						
Tertile 1	**29.8 (29.2; 30.2)**	Reference	**24.1 (23.5; 24.6)**	Reference	**5.7 (5.2; 6.2)**	Reference
Tertile 2	**31.7 (30.9; 32.6)**	**1.9 (1.1; 3.1)**	**25.4 (24.5; 26.2)**	1.3 (-0.0; 2.3)	**6.3 (5.6; 7.0)**	0.6 (-0.3; 1.4)
Tertile 3	**31.8 (30.9; 32.5)**	**2.0 (1.0; 2.8)**	**25.6 (24.6; 26.5)**	**1.5 (0.2; 2.6)**	**6.2 (5.5; 7.2)**	0.5 (-0.5; 1.4)
Women						
Tertile 1	**34.7 (34.2; 35.3)**	Reference	**30.0 (29.5; 30.5)**	Reference	**4.7 (4.2; 5.3)**	Reference
Tertile 2	**36.1 (35.4; 36.9)**	**1.4 (0.5; 2.4)**	**32.4 (31.5; 33.2)**	**2.4 (1.4; 3.3)**	**3.7 (3.0; 4.3)**	**-1.0 (-2.0; -0.1)**
Tertile 3	**36.1 (35.2; 36.8)**	**1.4 (0.2; 2.4)**	**30.9 (30.0; 32.0)**	0.9 (-0.2; 2.0)	**5.2 (4.4; 5.9)**	0.5 (-0.5; 1.2)
FT_4 tertiles						
Men						
Tertile 1	**32.8 (31.8; 34.0)**	Reference	**26.6 (25.6; 27.5)**	Reference	**6.2 (5.3; 7.1)**	Reference
Tertile 2	**31.2 (30.1; 32.6)**	-1.6 (-3.5; 0.2)	**25.4 (23.9; 26.8)**	-1.2 (-3.2; 0.5)	**5.8 (4.7; 7.0)**	-0.4 (-1.6; 1.0)
Tertile 3	**29.6 (28.5; 30.8)**	**-3.2 (-5.0; -1.4)**	**23.5 (22.3; 24.6)**	**-3.1 (-4.9;-1.4)**	**6.1 (5.0; 7.3)**	-0.1 (-1.7; 1.6)
Women						
Tertile 1	**37.5 (36.5; 38.7)**	Reference	**32.4 (31.5; 33.4)**	Reference	**5.1 (4.3; 6.1)**	Reference
Tertile 2	**35.9 (34.5; 37.6)**	-1.6 (-3.15; 0.0)	**31.0 (29.7; 32.4)**	-1.4 (-3.0; 0.2)	**4.9 (3.8; 6.2)**	-0.2 (-1.4; 1.1)
Tertile 3	**34.0 (32.8; 35.4)**	**-3.5 (-5.6; -1.5)**	**29.9 (28.7; 31.2)**	**-2.5 (-4.4;-0.7)**	**4.1 (3.3; 5.1)**	-1.0 (-2.4; 0.4)

*Data are given as years (95% confidence intervals). All life expectancies have been calculated with hazard ratios adjusted for age, cohort, smoking, alcohol intake, education level, marital status, diabetes mellitus, body mass index, systolic blood pressure, total cholesterol, triglycerides, use of antihypertensive medications, and use of lipid-lowering medications. †Differences in LE are calculated using the first tertile as reference. Abbreviations: LE, life expectancy; TSH, thyroid-stimulating hormone; FT_4, free thyroxine; CVD, cardiovascular disease.

with the lowest tertile, the highest FT_4 tertile was associated with a higher risk of incident CVD, meaning an earlier clinical manifestation of CVD and fewer years lived without CVD. The highest FT_4 tertile was also associated with an increased mortality risk among participants without CVD, resulting in a further decrease in total LE and LE without CVD. *LE with CVD* is the resultant of 2 components: risk of incident CVD (transition 1) and risk of mortality among subjects with CVD (transition 3). Compared with the lowest tertile, the highest FT_4 tertile was associated with a 1.32 times higher risk of incident CVD, meaning an earlier clinical manifestation of CVD and more years lived with CVD. However, participants with CVD in the highest FT_4 tertile had an even higher risk of mortality (ie, 1.64 times higher), which explains the decrease in the number of years lived with CVD.

Our study confirms prior research, suggesting that high-normal thyroid function is associated with an increased risk of CVD and mortality, independent of traditional cardiovascular risk factors.[2-5] Most importantly, it extends the previous literature by revealing considerable differences in LE within the reference range of thyroid function. These findings provide supporting evidence for a reevaluation of the current reference ranges of TSH and FT_4 measurements, implying the possibility of an upward shift of TSH and a downward shift of FT_4 reference ranges in middle-aged and elderly people. Further investigations are needed to determine the clinically relevant normal range of thyroid function.

Overactivity of thyroid gland is known to have a negative effect on overall health. Higher thyroid hormone concentrations have been associated with an increased heart rate (chronotropic effect), myocardial contractility (inotropic effect), and hypercoagulability, which may further predispose to CVD and mortality.[6,31] Moreover, elevated thyroid hormone levels can enhance oxygen consumption and production of reactive oxygen species, which may subsequently induce DNA damage and cell apoptosis.[32,33] Also, elevated thyroid hormone levels can affect cognition, nerve conduction, and bone mineral density, thus contributing to an increased risk of dementia, polyneuropathy, osteoporosis, and death.[34-36] However, the deleterious effects of high thyroid function could be also extended to the high-normal range of thyroid function.[2,37] Therefore, the aforementioned mechanisms could be additionally involved in the pathways linking high-normal thyroid function to a reduced life span.

Other mechanisms can explain the association of low-normal thyroid function with a prolonged life span. Low-normal thyroid function may promote energy conservation, which is necessary to adequately cope with acute and chronic stressors.[38] Low-normal thyroid function may also represent a heritable phenotype of exceptional longevity. In line with this hypothesis, Rozing et al[39] observed lower circulating thyroid hormone levels in middle-aged offspring of nonagenarian siblings compared with age-matched controls. In addition, decreased thyroid hormone levels in nonagenarian siblings have been associated with a prolonged life span in their parents.[40]

Based on the negative feedback mechanism of the hypothalamus-pituitary-thyroid axis, each individual is expected to have a unique set point of thyroid function, with an inverse relation between TSH and FT_4 concentrations. Our results were consistent with the feedback regulation because high-normal TSH levels and

low-normal FT_4 levels were both associated with an increased LE. However, LE in our participants was more strongly associated with FT_4 than with TSH levels. Likewise, previous cohort studies have reported a stronger association of adverse outcomes (including mortality) with FT_4 than with TSH levels, particularly within the euthyroid range.[2,4,13,14,22,35] Likely, genetic determinants and ageing can modify the TSH-FT_4 set point of the feedback mechanism among euthyroid individuals.[41,42] Various genetic polymorphisms that affect serum TSH but not FT_4 levels have been identified.[42]

In addition, we investigated the differences in LE with and without CVD among thyroid status categories (ie, hypothyroidism, euthyroidism, hyperthyroidism). In line with the results of our main analysis, we found that hypothyroid participants lived longer than euthyroid subjects. Among hyperthyroid participants, we observed sex differences in the number of years lived with and without CVD. However, these results should be interpreted with caution, owing to the relatively small number of participants with thyroid dysfunction and their increased susceptibility to receiving treatment and changing health behaviors over time. Future studies can explore more extensively the effect of thyroid disease on LE with and without CVD.

To the best of our knowledge, this is the first population-based cohort study that investigates differences in LE with and without CVD within the reference range of thyroid function. Strengths include the prospective study design, the long follow-up period, and the large number of participants with extensive and detailed information on covariates and outcomes. The large sample size allowed us to conduct multiple sensitivity analyses, which provided consistent findings. Events were adjudicated using standardized criteria.

Several limitations should also be considered. The Rotterdam Study includes predominantly whites older than 45 years; therefore, our findings require confirmation in other populations. Moreover, we lacked repeated measurements of thyroid function. Nevertheless, this is unlikely to have affected our results, given that the normal range of thyroid function is considered to be stable over time with a low intra-individual variability.[43] Furthermore, we did not have data available on serum triiodothyronine levels. However, TSH and FT_4 represent the most relevant measurements of thyroid function in clinical practice. Due to the observational character of our study, the possibility of residual confounding cannot be entirely ruled out.

Conclusions

At the age of 50 years, participants with low-normal thyroid function lived up to 3.5 years longer overall and up to 3.1 years longer without CVD than those with high-normal thyroid function. Our findings support a reevaluation of the current reference ranges of TSH and FT_4 measurements, implying the possibility of an upward shift of TSH and a downward shift of FT_4 current limits in middle-aged and elderly people. Future research is needed to replicate our findings and elucidate the exact mechanisms underlying the LE differences within the reference range of thyroid function.

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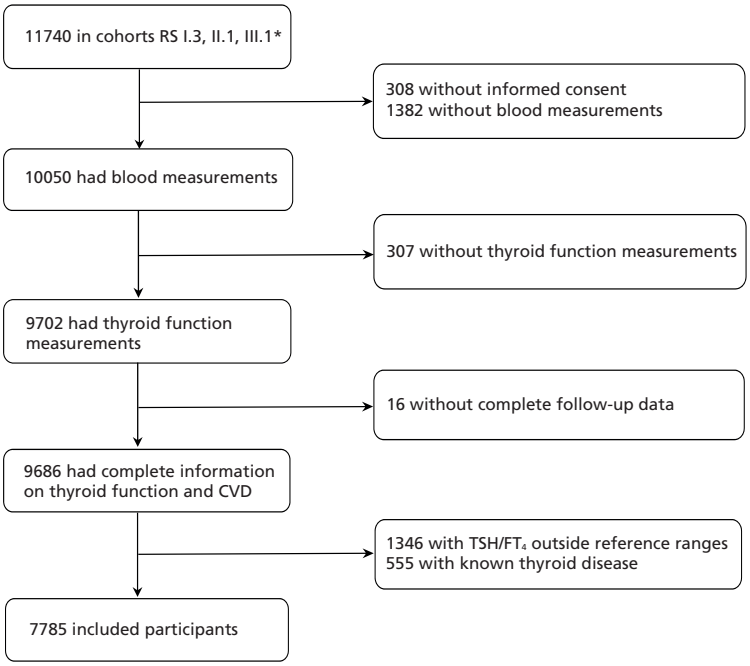
SUPPLEMENTAL MATERIAL

Supplemental Figure 1. Flow chart for the selection of study participants.



*A total of 11740 participants were enrolled during the third visit of the first cohort (n=4797) and the first visit of the second (n=3011) and third (n=3932) cohorts of the Rotterdam Study. Abbreviations: RS, Rotterdam Study; CVD, cardiovascular disease; TSH, thyroid-stimulating hormone; FT_4, free thyroxine.

Supplemental Table 1. HRs of incident CVD and death among TSH and FT_4 tertiles, excluding the first 2 years of follow-up for CVD and death

			TSH		FT_4	
Transition	**Cases/PY**	**TSH/FT_4 tertiles**	**HR (95% CI) Model 1**	**HR (95% CI) Model 2**	**HR (95% CI) Model 1**	**HR (95% CI) Model 2**
Incident CVD	610/38139	Tertile 1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
		Tertile 2	0.83 (0.69; 1.01)	0.84 (0.69; 1.02)	1.14 (0.94; 1.40)	1.14 (0.93; 1.40)
		Tertile 3	0.95 (0.79; 1.16)	0.96 (0.79; 1.17)	**1.25 (1.02; 1.53)**	**1.24 (1.02; 1.52)**
Mortality among those without CVD	639/39950	Tertile 1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
		Tertile 2	**0.78 (0.65; 0.94)**	**0.80 (0.67; 0.96)**	1.21 (0.98; 1.47)	1.19 (0.97; 1.46)
		Tertile 3	**0.72 (0.60; 0.88)**	**0.77 (0.63; 0.94)**	**1.43 (1.18; 1.74)**	**1.35 (1.11; 1.65)**
Mortality among those with CVD	425/7753	Tertile 1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
		Tertile 2	0.98 (0.78; 1.23)	0.92 (0.73; 1.16)	1.29 (1.00; 1.67)	**1.31 (1.01; 1.68)**
		Tertile 3	**0.77 (0.61; 0.98)**	**0.76 (0.60; 0.97)**	**1.49 (1.17; 1.89)**	**1.49 (1.17; 1.90)**

Model 1: age, sex, and cohort. Model 2: Model 1, smoking, alcohol intake, education level, marital status, diabetes mellitus, body mass index, systolic blood pressure, total cholesterol, triglycerides, use of antihypertensive medications, and use of lipid-lowering medications. Abbreviations: HR, hazard ratio; CVD, cardiovascular disease; TSH, thyroid-stimulating hormone; FT_4, free thyroxine; PY, person-years; CI, confidence interval.

Supplemental Table 2. HRs for incident CVD and death among TSH and FT_4 tertiles, excluding users of thyroid function-altering medications and additionally adjusting for prevalent cancer

			TSH	FT_4
Transition	**Cases/PY**	**TSH/FT_4 tertiles**	**HR (95% CI)**	**HR (95% CI)**
Incident CVD	763/37814	Tertile 1	1 (Reference)	1 (Reference)
		Tertile 2	0.87 (0.73; 1.03)	1.14 (0.95; 1.37)
		Tertile 3	0.94 (0.78; 1.12)	**1.32 (1.10; 1.57)**
Mortality among those without CVD	771/40460	Tertile 1	1 (Reference)	1 (Reference)
		Tertile 2	**0.78 (0.65; 0.91)**	1.16 (0.96; 1.39)
		Tertile 3	**0.76 (0.64; 0.91)**	**1.43 (1.20; 1.72)**
Mortality among those with CVD	524/8445	Tertile 1	1 (Reference)	1 (Reference)
		Tertile 2	0.93 (0.76; 1.15)	1.24 (0.98; 1.56)
		Tertile 3	**0.80 (0.65; 1.00)**	**1.57 (1.26; 1.94)**

Hazard ratios are adjusted for age, sex, cohort, smoking, alcohol intake, education level, marital status, diabetes mellitus, body mass index, systolic blood pressure, total cholesterol, triglycerides, use of antihypertensive medications, use of lipid-lowering medications, and prevalent cancer. Abbreviations: HR, hazard ratio; CVD, cardiovascular disease; TSH, thyroid-stimulating hormone; FT_4, free thyroxine; PY, person-years; CI, confidence interval.

Supplemental Table 3. LE at age 50 years, among TSH and FT_4 tertiles, in men and women over 8 years of follow-up*

	Total LE	Differences in total LE	Differences in LE free of CVD	Differences in LE with CVD
TSH tertiles				
Men				
Tertile 1	29.6	Reference	Reference	Reference
Tertile 2	32.3	2.7	1.4	1.3
Tertile 3	31.5	2.0	1.3	0.6
Women				
Tertile 1	34.6	Reference	Reference	Reference
Tertile 2	36.3	1.7	3.1	-1.3
Tertile 3	36.2	1.6	1.4	0.2
FT_4 tertiles				
Men				
Tertile 1	31.8	Reference	Reference	Reference
Tertile 2	30.5	-1.2	-0.9	-0.3
Tertile 3	28.8	-3.0	-2.8	-0.2
Women				
Tertile 1	37.9	Reference	Reference	Reference
Tertile 2	35.8	-2.1	-1.5	-0.6
Tertile 3	33.9	-4.0	-2.7	-1.3

*Data are given as years. Differences are calculated using the first tertile as reference. All LEs have been calculated with hazard ratios adjusted for age, cohort, smoking, alcohol intake, education level, marital status, diabetes mellitus, body mass index, systolic blood pressure, total cholesterol, triglycerides, use of antihypertensive medications, and use of lipid-lowering medications. Abbreviations: LE, life expectancy; TSH, thyroid-stimulating hormone; FT_4, free thyroxine; CVD, cardiovascular disease.

Supplemental Table 4. LE at age 50 years, among thyroid status categories, in men and women*

	TN	Total LE	Differences in total LE	Differences in LE free of CVD	Differences in LE with CVD
Men					
Euthyroidism	3667	**31.0 (30.8; 31.3)**	Reference	Reference	Reference
Hypothyroidism†	245	**31.3 (29.5; 32.9)**	0.3 (-1.7; 1.9)	0.1 (-2.4; 2.5)	0.2 (-1.5; 2.1)
Hyperthyroidism†	80	**29.6 (26.6; 32.9)**	-1.4 (-4.4; 2.0)	-3.7 (-7.6; 0.1)	2.3 (-1.3; 6.4)
Women					
Euthyroidism	4028	**35.6 (35.3; 35.9)**	Reference	Reference	Reference
Hypothyroidism†	551	**36.7 (35.5; 37.8)**	1.1 (-0.4; 2.3)	0.8 (-0.7; 2.2)	0.3 (-0.8; 1.3)
Hyperthyrodism†	110	**36.0 (33.7; 38.4)**	0.4 (-2.1; 2.9)	**2.3 (0.2; 4.4)**	**-1.9 (-3.1;-0.4)**

*For this analysis, we included participants without known thyroid disease and not using thyroid function-altering medications (ie, thyroid medications, amiodarone, corticosteroids). Differences are calculated using the euthyroid category as reference. Data are given as years (95% confidence intervals). All LEs have been calculated with hazard ratios adjusted for age, cohort, smoking, alcohol intake, education level, marital status, diabetes mellitus, body mass index, systolic blood pressure, total cholesterol, triglycerides, use of antihypertensive medications, and use of lipid-lowering medications. †Includes subclinical and clinical range. Abbreviations: LE, life expectancy; TN, total number; CVD, cardiovascular disease.

CHAPTER 3.4

DIFFERENCES IN TOTAL LIFE EXPECTANCY AND LIFE EXPECTANCY WITH AND WITHOUT NON-COMMUNICABLE DISEASES WITHIN THE REFERENCE RANGE OF THYROID FUNCTION

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Manuscript in preparation

The author list may change according to contributions after the printing of this thesis.

ABSTRACT

Background Variations in thyroid function within the reference range are associated with an increased risk of diseases and death. However, the impact of thyroid function on life expectancy (LE) and the number of years lived with and without non-communicable diseases (NCD) remains unknown. Therefore, we aimed to investigate the association of thyroid function with total LE and LE with and without NCD among euthyroid subjects.

Methods Participants of the Rotterdam Study without known thyroid disease and with thyroid-stimulating hormone (TSH) and free thyroxine (FT_4) levels within the reference ranges were eligible. NCD was defined as presence of cardiovascular disease, diabetes mellitus type 2, or cancer. We used multistate life tables to calculate the total LE and LE with and without NCD among TSH and FT4 tertiles, in men and women. LE estimates were obtained using prevalence, incidence rates and hazard ratios for three transitions (healthy to NCD, healthy to death and NCD to death). Analyses were adjusted for sociodemographic and cardiovascular risk factors.

Results The mean (standard deviation) age of 7644 participants was 64.5 (9.7) years and 52.2% were women. Over a median follow-up of 8 years, we observed 1396 incident NCD events and 1422 deaths. Compared with those in the lowest tertile, men and women in the highest TSH tertile lived 1.5 (95% confidence interval [95% CI], 0.8 to 2.3) and 1.5 (95% CI, 0.8 to 2.2) years longer, respectively; of which 1.4 (95% CI, 0.5 to 2.3) and 1.3 (95% CI, 0.3 to 2.1) years with NCD. Compared with those in the lowest tertile, the difference in LE for men and women in the highest FT_4 tertile was -3.7 (95% CI,-5.1 to -2.2) and -3.3 (95% CI, -4.7 to -1.9), respectively; of which -1.8 (95% CI, -3.1 to -0.7) and -2.0 (95% CI, -3.4 to -0.7) years without NCD.

Conclusions There are meaningful differences in total LE, LE with and without NCD within the reference ranges of thyroid function. These findings support a reevaluation of the current reference ranges of thyroid function.

INTRODUCTION

Non-communicable diseases (NCD) pose a global health threat, inflicting high disability rates and a huge economic burden.[1,2] According to the World Health Organization, NCD are a leading cause of deaths, accounting for approximately 65% of total mortality worldwide.[2,3] Cardiovascular disease (CVD), diabetes, cancer, and chronic kidney disease (CKD) account for a large proportions of deaths.[4] Among other factors, clinical and subclinical thyroid dysfunction are associated with the development of NCD and the risk of NCD mortality.[5-9]

In view of the ongoing debate on redefining the reference ranges of thyroid-stimulating hormone (TSH) and free thyroxine (FT_4) levels,[10] many prospective studies have suggested that variations in thyroid function within the reference range can contribute to the occurrence of chronic conditions and deaths.[11-13] Recently, it was reported that middle-aged and older adults with low-normal thyroid function have a longer total life expectancy (LE) and a longer LE without CVD than those with high-normal thyroid function.[14] Still, it remains unclear whether these differences in LE within the reference range of thyroid function reflect healthy years or years lived with NCD. Prospective studies in euthyroid subjects have suggested that high-normal thyroid function increases the risk of CVD, cancer or CKD,[12,13,15-17] while low-normal thyroid function has been associated with an increased risk of chronic metabolic diseases as diabetes.[11,18] Based on this evidence, it is challenging to determine the balance of overall benefits and risks for specific cutoffs of TSH and FT_4 levels within the reference range. In this respect, the utilization of multidimensional measures, as LE with and without NCD, can provide useful information on the qualitative and quantitative impact of thyroid function on general health.

In a large prospective population-based cohort study, we investigated the association of thyroid function within the reference range with the risk of incident NCD. Also, we investigated whether there are differences in the amount of years lived with and without NCD, within the reference range of thyroid function. We focused on chronic conditions that have been prospectively associated with thyroid function,[11,13,14] and have been highlighted as a global threat by the United Nations.[19] NCD was defined as the presence of CVD, diabetes, or cancer. Due to the incomplete data on the CKD diagnosis, we performed a secondary analysis which additionally included CKD in the definition of NCD.

METHODS

Study population

The Rotterdam Study is a large prospective population-based cohort study. The objectives and design have been described in detail previously.[20] The Rotterdam Study was initiated in 1989, including 7983 participants aged 55 years or older. In 2000, the study was extended with a second cohort of 3011 subjects. In 2006, a third cohort of 3932 subjects aged 45 years or older was added. Study participants undergo extensive follow-up medical examinations every 3 to 5 years. Baseline measurements for our study were performed during the third visit of the first cohort (1997-1999, n=4797) and the first visit of the second (2000-2001, n=3011) and third (2006-2008, n=3932) cohorts of the Rotterdam Study. The original cohort during these three visits included a total of 11740 participants, of which 10050 had available blood measurements. Thyroid function measurements were performed in a random sample of 9702 participants. Of these, we excluded 836 participants with past thyroid disease or taking thyroid medications, 182 participants without complete information on prevalent or incident NCD, and 1040 participants with TSH or FT_4 outside the normal reference ranges. The remaining 7644 participants were eligible for the analyses.

The protocols of the Rotterdam Study have been approved by the Medical Ethics Committee of the Erasmus University and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the Population Study Act Rotterdam Study. In accordance with the Declaration of Helsinki, all included participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

Assessment of thyroid function

Thyroid function was assessed at baseline during the third visit of the first cohort (RS I.3) and the first visit of the second (RS II.1) and third (RS III.1) cohorts using the same method and assay. Measurements of TSH and FT_4 were performed in baseline serum samples stored at -80°C using the electrochemiluminescence immunoassay ECLIA Roche. The reference ranges of TSH (0.40–4.0 mIU/L) and FT_4 (0.86–1.94 ng/dL, alternatively 11–25 pmol/L) were determined based on national guidelines and our previous studies.[17,18] Participants and family physicians were not informed about the thyroid function measurements results. The study investigators assessing the outcomes of interest were blinded to the thyroid status of participants.

Assessment of NCD and mortality

Outcome measures were incident nonfatal NCD, mortality among those with NCD and overall mortality. NCD was defined as presence of CVD, diabetes mellitus type 2, or cancer.

CVD was defined as presence of coronary heart disease, stroke or heart failure. Coronary heart disease was defined as coronary revascularization (as a proxy for significant coronary artery disease), fatal or nonfatal myocardial infarction or fatal coronary heart disease.[21] Based on the World Health Organization criteria, stroke was defined as a syndrome of rapidly developing symptoms, with an apparent vascular cause of focal or global cerebral dysfunction lasting 24 hours or longer or leading to death.[22] Based on the European Society of Cardiology criteria, heart failure was defined as the presence of typical symptoms and signs, as breathlessness at rest or during exertion, ankle edema, and pulmonary crepitations, confirmed by the objective evidence of cardiac dysfunction (ie, chest X-ray, echocardiography) or a positive response to the initiated treatment.[23] Prevalent CVD was assessed at baseline through interview and medical records. After enrollment, participants were continuously monitored for incident CVD through linkage of the study database with files from general practitioners and hospital records.

Diabetes mellitus was defined as fasting serum glucose level of 7 mmol/L or more, non-fasting plasma glucose level of 11.1 mmol/L or more (when fasting samples were absent) or the use of blood glucose lowering medications. Cases of type 2 diabetes were ascertained at baseline and during follow-up through general practitioners, hospital discharge letters, and serum glucose measurements from the Rotterdam Study visits. Information regarding the use of blood glucose lowering medications was derived from both structured home interviews and linkage to pharmacy records. Potential events of type 2 diabetes were independently adjudicated by two research physicians. In case of discrepancy, consensus was sought or an endocrinologist decided.[24]

Cancer events were classified according to the International Classification of Diseases (ICD) 10th edition. Cases of cancer were determined through general practitioners, hospital discharge letters and by linkage with a nationwide registry of histopathology and cytopathology in the Netherlands, Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief (PALGA).[25] Two research physicians independently assessed the diagnosis of cancer. In case of discrepancy, consensus was sought or a cancer epidemiologist decided.

Chronic kidney disease

Creatinine measurements were calibrated by aligning the mean values of creatinine with creatinine values of participants of the National Health and Nutrition Examination Survey III in different sex and age groups (<60, 60–69, and ≥70 years old).[26] Estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration Equation.[27] To calculate the annual eGFR decline, we first subtracted the eGFR estimates of the follow-up examination from the eGFR estimates at baseline and then divided by the time between the two visits. CKD was defined as eGFR<60 ml/min per 1.73 m^2. Patients with incident CKD were defined as individuals free of CKD at baseline (eGFR>60 ml/min per 1.73 m^2) who had a decline in eGFR to <60 ml/min per 1.73 m^2 between the two periodic examinations.[28] To estimate the censoring date of the cases, we assumed a linear decrease in eGFR. Given this assumption, the date that each case had passed the eGFR threshold of 60 ml/min per 1.73 m^2 was taken as the censoring date and it was used to calculate the follow-up time for incident cases. For controls, the time spent between the two examinations was used as the follow-up time.

Additional measurements

The baseline home interview provided information on medical history, medication use, tobacco smoking, alcohol consumption, education level and marital status.[20] Smoking habits were categorized as current, former and never smoking. Education level was divided into four categories: elementary, lower secondary, higher secondary and tertiary education, in accordance with the standard international classification of education. Marital status was categorized as single, married, widowed and divorced/separated. Lipid levels were measured by an automated enzymatic procedure (Mannheim System). Anthropometric measurements were performed in the research center by trained medical staff. Body mass index was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured in the sitting position on the right arm and calculated as the mean of two measurements using a random-zero sphygmomanometer.

Statistical analysis

Total LE and the number of years lived with and without NCD were calculated among tertiles of TSH and FT_4, by using multistate lifetables.[29] Differences in LE were evaluated using the lowest tertile as reference. Multistate life tables combined

information from participants in 3 possible health states, namely "free of NCD", "NCD", and "death". Possible transitions of participants were: (1) from free of NCD to NCD (incident NCD); (2) from free of NCD to death (mortality among those without NCD); (3) from NCD to death (mortality among those with NCD). Backflows were not allowed and only the first event into a state was considered.[30] To calculate LE, we followed a similar approach to previous studies.[29,31] Due to the known gender differences in LE, analyses were performed separately among men and women. We first calculated the prevalence of TSH tertiles among participants with and without NCD, categorized in 10-year age groups. In each transition, we calculated age-specific incidence rates. Next, we applied Poisson regression with Gompertz distribution to compute hazard ratios (HRs) of the association between TSH tertiles and incident NCD or mortality, adjusting for potential confounders. The confidence intervals of LE estimates were calculated using Monte Carlo method with 10000 bootstrap simulations.[32] Furthermore, we repeated the analyses for the FT_4 tertiles.

Confounders were selected on the basis of biological plausibility and previous literature. Model 1 was adjusted for age, sex, and cohort. Model 2 was additionally adjusted for smoking, alcohol intake, education level, marital status, body mass index, systolic blood pressure, total cholesterol, triglycerides, and use of antihypertensive and lipid-lowering medications.

Multiple imputations were performed in case of missing covariates (<5% for all covariates). Statistical analyses were conducted using IBM SPSS version 21 (IBM Corp), STATA version 13 for Windows (StataCorp, College Station, Texas) and @RISK software (Palisade).

Several sensitivity analyses were performed: (1) To account for potential reverse causation, we excluded NCD events or deaths that occurred during the first 2 years of follow-up. (2) We excluded participants using thyroid function-altering medications, as amiodarone or corticosteroids. (3) To detect a potential influence of follow-up duration on our results, we performed the analyses restricting the length of follow-up to 8 years (median follow-up time). (4) We additionally included CKD in the definition of NCD. (5) Chronic obstructive pulmonary disease (COPD) was not included in the primary outcome of NCD, due to the lack of solid evidence on the association of thyroid function with incident COPD. However, we performed a sensitivity analysis in which we included COPD in the definition of NCD. COPD was diagnosed based on an obstructive pre-bronchodilator spirometry (FEV_1/FVC <0.70) according to the GOLD guidelines.[33] The incident date of COPD was defined as the

date of the first obstructive lung function examination, the date of COPD diagnosis in the medical records or the date of the first prescription of COPD medications, whichever came first. (6) Lastly, we assessed the differences in LE with and without CVD, diabetes, and cancer, separately, among the TSH and FT_4 tertiles.

RESULTS

Baseline characteristics of 7644 eligible participants are presented in Table 1. The mean (standard deviation) age of participants was 64.5 (9.7) years and 52.3% were women. Over a median follow-up time of 8 years, 1396 incident NCD events and 1422 deaths occurred. Both models yielded similar estimates, therefore we further report the results of the most adjusted model (Model 2).

Table 1. Baseline characteristics of 7644 participants

	Men	Women
Number	3647	3997
Age, years	64.2 (9.2)	64.8 (10.1)
Smoking, n (%)		
current	897 (24.6)	810 (20.3)
former	2143 (58.8)	1512 (37.8)
never	607 (16.6)	1675 (41.9)
Education, n (%)		
Elementary	332 (9.1)	588 (14.7)
Lower secondary	1041 (28.5)	2012 (50.3)
Higher secondary	1335 (36.6)	900 (22.5)
Tertiary	939 (25.7)	497 (12.4)
Marital status, n (%)		
Single	115 (3.2)	244 (6.1)
Married	3113 (85.4)	2474 (61.9)
Widowed	222 (6.1)	870 (21.8)
Divorced/Separated	197 (5.4)	409 (10.2)
BMI, kg/m^2	27.0 (3.5)	27.3 (4.6)
Systolic blood pressure, mm Hg	141.0 (20.3)	137.8 (21.5)
Use of antihypertensive medications, n (%)	811 (22.2)	927 (23.2)
Total cholesterol, mmol/l	5.4 (0.9)	5.9 (0.9)
Triglycerides, mmol/l	1.6 (0.9)	1.5 (0.7)
Use of lipid-lowering medications, n (%)	662 (18.2)	576 (14.4)
TSH, mIU/L, median (IQR)	1.8 (1.2-2.4)	1.9 (1.3-2.6)
FT_4, pmol/L	15.9 (2.0)	15.6 (1.9)

Data are mean (sd), unless otherwise specified. Abbreviations: sd, standard deviation; BMI, body-mass index; TSH, thyroid-stimulating hormone; IQR, interquartile range; FT_4, free thyroxine.

Association of thyroid function within the reference range with the risk of NCD and death

The association of TSH tertiles with the risk of incident NCD was not statistically significant (Table 2). Compared with the lowest tertile, the highest TSH tertile was associated with a lower risk of mortality among participants without NCD (HR, 0.67; 95% CI, 0.54 to 0.83) (Table 2). Also, there was a borderline statistically significant association between the highest TSH tertile and a lower risk of mortality among participants with NCD (HR, 0.88; 95% CI, 0.75 to 1.03) (Table 2).

The highest FT_4 tertile was associated with a 1.17 times higher risk of incident NCD than the lowest tertile (95% CI, 1.02 to 1.34) (Table 2). The highest FT_4 tertile was also associated with a 1.56 times higher risk of mortality among participants with NCD (95% CI, 1.32 to 1.85) and a 1.44 times higher risk of mortality among participants without NCD (95% CI, 1.15 to 1.79) (Table 2), compared with the lowest tertile.

Results for TSH and FT_4 analyses remained similar after excluding the events that occurred during the first 2 years of follow-up (Supplemental Table 1) and after excluding users of thyroid function-altering medications (Supplemental Table 1).

Table 2. HRs for incident NCD* and death among TSH and FT_4 tertiles

			TSH		FT_4	
Transition	**Cases/PY**	**TSH/FT_4 tertiles**	**Model 1 HR (95% CI)**	**Model 2 HR (95% CI)**	**Model 1 HR (95% CI)**	**Model 2 HR (95% CI)**
Incident NCD	1396/27705	Tertile 1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
		Tertile 2	0.98 (0.86; 1.11)	0.98 (0.86; 1.12)	**1.16 (1.01; 1.32)**	**1.17 (1.02; 1.33)**
		Tertile 3	1.05 (0.92; 1.19)	1.05 (0.92; 1.19)	**1.17 (1.02; 1.33)**	**1.17 (1.02; 1.34)**
Mortality among those without NCD	532/32828	Tertile 1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
		Tertile 2	**0.68 (0.55; 0.83)**	**0.70 (0.56; 0.85)**	1.21 (0.96; 1.51)	1.20 (0.95; 1.50)
		Tertile 3	**0.64 (0.52; 0.79)**	**0.67 (0.54; 0.83)**	**1.52 (1.22; 1.88)**	**1.44 (1.15; 1.79)**
Mortality among those with NCD	890/18456	Tertile 1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
		Tertile 2	0.90 (0.77; 1.06)	0.91 (0.78; 1.06)	**1.23 (1.03; 1.47)**	**1.24 (1.04; 1.47)**
		Tertile 3	**0.84 (0.72; 0.99)**	0.88 (0.75; 1.03)	**1.59 (1.35; 1.88)**	**1.56 (1.32; 1.85)**

*NCD includes cardiovascular disease, diabetes mellitus, and cancer. Model 1: age, sex, and cohort. Model 2: Model 1, smoking, alcohol intake, education level, marital status, body mass index, systolic blood pressure, total cholesterol, triglycerides, use of antihypertensive medications, and use of lipid-lowering medications. Abbreviations: HR, hazard ratio; TSH, thyroid-stimulating hormone; FT_4, free thyroxine; PY, person-years; CI, confidence interval; NCD, non-communicable diseases.

Association of thyroid function within the reference range with total LE and LE with and without NCD

Total LE increased significantly from the lowest to the middle TSH tertile and did not change substantially from the middle to the highest TSH tertile. Compared with those in the lowest tertile, men in the highest TSH tertile lived 1.5 (95% CI, 0.8 to 2.3) years longer overall, of which 0.1 (95% CI, -0.8 to 1.2) years longer without NCD and 1.4 (95% CI, 0.5 to 2.3) years longer with NCD (Table 3). Compared with those in the lowest tertile, women in the highest TSH tertile lived 1.5 (95% CI, 0.8 to 2.2) years longer overall, of which, 0.2 (95% CI, -0.8 to 1.3) years longer without NCD and 1.3 (95% CI, 0.3 to 2.1) years longer with NCD (Table 3).

Table 3. LE with and without NCD* at age 50 among TSH and FT_4 tertiles, in men and women

TSH/FT_4 tertiles	Differences in total LE†	Differences in LE free of NCD†	Differences in LE with NCD†
TSH tertiles			
Men			
Tertile 1	Reference	Reference	Reference
Tertile 2	**1.4 (0.5; 2.1)**	0.6 (-0.3; 1.4)	0.8 (-0.1; 1.8)
Tertile 3	**1.5 (0.8; 2.3)**	0.1 (-0.8; 1.2)	**1.4 (0.5; 2.3)**
Women			
Tertile 1	Reference	Reference	Reference
Tertile 2	**1.4 (0.6; 2.0)**	0.7 (-0.2; 1.6)	0.7 (-0.2; 1.5)
Tertile 3	**1.5 (0.8; 2.2)**	0.2 (-0.8; 1.3)	**1.3 (0.3; 2.1)**
FT_4 tertiles			
Men			
Tertile 1	Reference	Reference	Reference
Tertile 2	**-2.0 (-3.4;-0.7)**	**-1.6 (-2.8;-0.5)**	-0.4 (-1.6; 0.9)
Tertile 3	**-3.7 (-5.1;-2.2)**	**-1.8 (-3.1;-0.7)**	**-1.9 (-3.4;-0.3)**
Women			
Tertile 1	Reference	Reference	Reference
Tertile 2	**-1.8 (-3.0;-0.7)**	**-1.7 (-2.9;-0.6)**	-0.1 (-1.1; 1.2)
Tertile 3	**-3.3 (-4.7;-1.9)**	**-2.0 (-3.4;-0.7)**	-1.3 (-2.7; 0.2)

*NCD includes cardiovascular disease, diabetes mellitus, and cancer. Data are given as years (95% confidence intervals). †Differences in LE are calculated using the first tertile as reference. All life expectancies have been calculated with hazard ratios adjusted for age, cohort, smoking, alcohol intake, education level, marital status, body mass index, systolic blood pressure, total cholesterol, triglycerides, use of antihypertensive medications, and use of lipid-lowering medications. Abbreviations: LE, life expectancy; TSH, thyroid-stimulating hormone; FT_4, free thyroxine; NCD, non-communicable diseases.

Total LE decreased progressively with increasing FT_4 tertiles (Table 3). Compared with those in the lowest tertile, the difference in LE for men in the highest FT_4 tertile was -3.7 (95% CI, -5.1 to -2.2) years overall, of which -1.8 (95% CI, -3.1 to -0.7) years without NCD and -1.9 (95% CI, -3.4 to -0.3) years with NCD (Table 3). Compared with those in the lowest tertile, the difference in LE for women in the highest FT_4 tertile was -3.3 (95% CI, -4.7 to -1.9) years overall, of which -2.0 (95% CI, -3.4 to -0.7) years without NCD and -1.3 (95% CI, -2.7 to 0.2) years with NCD (Table 3). Results remained similar over the length of follow-up of 8 years (Supplemental Table 2) or after including CKD in the definition of NCD (Supplemental Table 3) or after including COPD in the definition of NCD (Supplemental Table 4). Compared with those in the lowest tertile, men and women in the highest FT_4 tertile lived less years free of CVD, diabetes, and cancer, respectively (Supplemental Tables 5-7).

DISCUSSION

In this large prospective population-based cohort study among middle-aged and older adults, we found meaningful differences in LE with and without NCD within the reference ranges of thyroid function. Participants with low-normal FT_4 levels lived up to 3.7 years longer overall, of which up to 1.9 years longer without NCD than those with high-normal FT_4 levels. Participants with high-normal TSH levels lived up to 1.5 years longer overall, of which up to 1.4 years longer with NCD than those with low-normal TSH levels. No meaningful sex differences throughout the TSH and FT_4 tertiles were observed.

Another study from our group previously reported meaningful differences in total LE and LE without CVD within the reference ranges of TSH and FT_4 levels.[14] Meanwhile, the present study provides a broader perspective by using the multidimensional measure of LE with and without NCD. Importantly, our findings reinforce the idea of qualitative and quantitative differences within the reference range of thyroid function. Furthermore, our results support a reevaluation of the reference ranges of thyroid function in middle-aged and older adults, implying the possibility of a downward shift in the FT_4 current limits.

Previous studies have suggested that the beneficial effects of high-normal thyroid function on metabolism can be counterbalanced by detrimental effects on other systems, such as the cardiovascular system.[11,14,17,18] In this context, our study sheds light onto the resultant of the system-specific effects of thyroid function,

suggesting that the overall risk of NCD increases in the high-normal range of FT_4 levels. However, the life expectancy estimates are not only attributable to the risk of developing the diseases, but also depend on the risk of dying before developing the diseases and the risk of dying after developing the diseases. In line with previous studies conducted in middle-aged and elderly, we showed that high-normal thyroid function is associated with an increased risk of mortality.[14,34,35] This was further translated into a decreased LE with and without NCD related to the high-normal range of thyroid function.

More specifically, *LE without NCD* is the resultant of 2 components: risk of incident NCD (transition 1) and risk of mortality among participants without NCD (transition 2). Compared with the lowest tertile, the highest FT_4 tertile was associated with a higher risk of incident NCD, meaning an earlier clinical manifestation of NCD and fewer years lived without NCD. The highest FT_4 tertile was also associated with an increased mortality risk among participants without NCD, resulting in a further decrease in total LE and LE without NCD. *LE with NCD* is the resultant of 2 components: risk of incident NCD (transition 1) and risk of mortality among participants with NCD (transition 3). Compared with the lowest tertile, the highest FT_4 tertile was associated with a 1.17 times higher risk of incident NCD, meaning an earlier clinical manifestation of NCD and more years lived with NCD. However, participants with NCD in the highest FT_4 tertile had an even higher risk of mortality (ie, 1.56 times higher), which explains the decrease in the number of years lived with NCD.

Our sensitivity analyses indicate that the estimates of LE with and without NCD reflect the combination of all NCD, and are not driven by one chronic disease alone. In a consistent manner, participants with low-normal thyroid function lived more years with CVD, diabetes, and cancer, respectively, than those with high-normal thyroid function. Besides, participants with low-normal thyroid function lived more years without CVD, diabetes, and cancer, respectively, than those with high-normal thyroid function. Together, these differences in the number of years lived with and without diseases contributed to the total differences in life expectancy within the reference range of thyroid function.

To the best of our knowledge, this is the first population-based cohort study that investigates the association between thyroid function and the risk of incident NCD. Also, this is the first study that examines the differences in LE with and without NCD within the reference range of thyroid function. We included a large number of participants with extensive and detailed information on covariates including exposures,

outcomes, and potential confounders. Events were adjudicated using standardized criteria. Another strength of our study is the prospective design with a long follow-up period. Thyroid function measurements were performed before the occurrence of incident NCD events. The possibility of reverse causation was taken into account by excluding the events that occurred during the first 2 years of follow-up. Multiple sensitivity analyses provided consistent findings.

Several limitations should also be considered. Due to the incomplete information on CKD, we could not include CKD in the primary outcome of NCD. The eGFR measurements were performed only twice, and the exact date of incident CKD was uncertain. However, we used the repeated measurements of eGFR to determine the slope of eGFR changes over time. Our results remained similar after including CKD in the definition of NCD. Moreover, we did not have data available on serum triiodothyronine levels. Nevertheless, TSH and FT_4 represent the most relevant measurements of thyroid function in clinical practice. Also, we lacked repeated measurements of thyroid function. However, it has been shown that studies using only one measurement of TSH and FT_4 can underestimate the association of thyroid function with morbidity and mortality by approximately one third, due to the regression dilution bias.[36] Thus, repeated measurements of thyroid function would be expected to strengthen our risk estimates. Besides, the possibility of residual confounding cannot be entirely ruled out due to the observational character of our study. Lastly, the Rotterdam Study includes predominantly white participants older than 45 years. Therefore, our findings need to be confirmed in other populations with similar characteristics to our population, as well as in other ethnicities and younger individuals.

Conclusions

In a population of middle-aged and older euthyroid subjects, we found that high-normal FT_4 levels were associated with an increased risk of incident NCD. Furthermore, we found meaningful differences in LE with and without NCD within the reference ranges of TSH and FT_4 levels. These results support a reevaluation of the current reference ranges of thyroid function. Future research is needed to replicate our findings, establish causality and elucidate the exact underlying mechanisms.

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. HRs for incident NCD and death among TSH and FT_4 tertiles, after excluding the first 2 years of follow-up for NCD and death or after excluding the users of thyroid function-altering medications

		After excluding the first 2 years of follow-up for NCD and death			After excluding the users of thyroid function-altering medications		
Transition	TSH/FT_4 tertiles	Cases/PY	TSH HR (95% CI)	FT_4 HR (95% CI)	Cases/PY	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Incident NCD	Tertile 1	1036/27312	1 (Reference)	1 (Reference)	1365/27334	1 (Reference)	1 (Reference)
	Tertile 2		0.92 (0.79; 1.06)	**1.18 (1.01; 1.37)**		**1.16 (1.00; 1.35)**	**1.18 (1.01; 1.37)**
	Tertile 3		1.02 (0.88; 1.18)	1.16 (1.00; 1.35)		1.16 (0.99; 1.34)	1.16 (1.00; 1.35)
Mortality among those without NCD	Tertile 1	385/30677	1 (Reference)	1 (Reference)	515/32341	1 (Reference)	1 (Reference)
	Tertile 2		**0.77 (0.60; 0.99)**	1.29 (0.99; 1.68)		1.29 (0.99; 1.68)	1.29 (0.99; 1.68)
	Tertile 3		**0.67 (0.51; 0.88)**	**1.42 (1.09; 1.84)**		**1.51 (1.18; 1.96)**	**1.42 (1.09; 1.84)**
Mortality among those with NCD	Tertile 1	682/16599	1 (Reference)	1 (Reference)	849/17991	1 (Reference)	1 (Reference)
	Tertile 2		0.90 (0.75; 1.07)	**1.27 (1.04; 1.56)**		**1.27 (1.04; 1.56)**	**1.27 (1.04; 1.56)**
	Tertile 3		**0.80 (0.66; 0.97)**	**1.55 (1.27; 1.87)**		**1.57 (1.30; 1.90)**	**1.55 (1.27; 1.87)**

Analyses were adjusted for age, sex, cohort, smoking, alcohol intake, education level, marital status, body mass index, systolic blood pressure, total cholesterol, triglycerides, use of antihypertensive medications, and use of lipid-lowering medications. Abbreviations: HR, hazard ratio; TSH, thyroid-stimulating hormone; FT_4, free thyroxine; PY, person-years; CI, confidence interval; NCD, non-communicable diseases.

Supplemental Table 2. LE at age 50 years, among TSH and FT_4 tertiles, in men and women over 8 years of follow-up

	Differences in total LE	Differences in LE free of NCD	Differences in LE with NCD
TSH tertiles			
Men			
Tertile 1	Reference	Reference	Reference
Tertile 2	1.8	0.3	1.5
Tertile 3	1.6	0	1.6
Women			
Tertile 1	Reference	Reference	Reference
Tertile 2	1.7	0.5	1.2
Tertile 3	1.5	0.1	1.4
FT_4 tertiles			
Men			
Tertile 1	Reference	Reference	Reference
Tertile 2	-1.6	-1.1	-0.4
Tertile 3	-3.5	-1.7	-1.8
Women			
Tertile 1	Reference	Reference	Reference
Tertile 2	-1.4	-1.2	-0.2
Tertile 3	-3.1	-1.9	-1.3

Data are given as years. Differences in LE are calculated using the first tertile as reference. All life expectancies have been calculated with hazard ratios adjusted for age, cohort, smoking, alcohol intake, education level, marital status, diabetes mellitus, body mass index, systolic blood pressure, total cholesterol, triglycerides, use of antihypertensive medications, and use of lipid-lowering medications. Abbreviations: LE, life expectancy; TSH, thyroid-stimulating hormone; FT_4, free thyroxine; NCD, non-communicable diseases.

Supplemental Table 3. LE with and without NCD* at age 50 years among TSH and FT_4 tertiles, in men and women

TSH/FT_4 tertiles	Differences in total LE	Differences in LE free of NCD	Differences in LE with NCD
TSH tertiles			
Men			
Tertile 1	Reference	Reference	Reference
Tertile 2	1.5	0.2	1.3
Tertile 3	1.8	0.1	1.6
Women			
Tertile 1	Reference	Reference	Reference
Tertile 2	1.5	0.3	1.1
Tertile 3	1.7	0.2	1.5
FT_4 tertiles			
Men			
Tertile 1	Reference	Reference	Reference
Tertile 2	-2.0	-1.3	-0.7
Tertile 3	-3.7	-1.7	-2.0
Women			
Tertile 1	Reference	Reference	Reference
Tertile 2	-1.7	-1.4	-0.2
Tertile 3	-3.3	-1.9	-1.4

*NCD includes cardiovascular disease, diabetes mellitus, cancer, and chronic kidney disease. Data are given as years. Differences in LE are calculated using the first tertile as reference. All life expectancies have been calculated with hazard ratios adjusted for age, cohort, smoking, alcohol intake, education level, marital status, body mass index, systolic blood pressure, total cholesterol, triglycerides, use of antihypertensive medications, and use of lipid-lowering medications. Abbreviations: LE, life expectancy; TSH, thyroid-stimulating hormone; FT_4, free thyroxine; NCD, non-communicable diseases.

Supplemental Table 4. LE with and without NCD* at age 50 years among TSH and FT_4 tertiles, in men and women

TSH/FT_4 tertiles	Differences in total LE	Differences in LE free of NCD	Differences in LE with NCD
TSH tertiles			
Men			
Tertile 1	Reference	Reference	Reference
Tertile 2	1.6	1.0	0.6
Tertile 3	1.5	0.1	1.4
Women			
Tertile 1	Reference	Reference	Reference
Tertile 2	1.5	1.2	0.4
Tertile 3	1.5	0.3	1.2
FT_4 tertiles			
Men			
Tertile 1	Reference	Reference	Reference
Tertile 2	-1.9	-1.3	-0.6
Tertile 3	-3.6	-1.7	-1.9
Women			
Tertile 1	Reference	Reference	Reference
Tertile 2	-1.7	-1.5	-0.2
Tertile 3	-3.1	-1.9	-1.2

*NCD includes cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, and cancer. Data are given as years (95% confidence intervals). †Differences in LE are calculated using the first tertile as reference. All life expectancies have been calculated with hazard ratios adjusted for age, cohort, smoking, alcohol intake, education level, marital status, body mass index, systolic blood pressure, total cholesterol, triglycerides, use of antihypertensive medications, and use of lipid-lowering medications. Abbreviations: LE, life expectancy; TSH, thyroid-stimulating hormone; FT_4, free thyroxine; NCD, non-communicable diseases.

Supplemental Table 5. LE with and without CVD at age 50 years among TSH and FT_4 tertiles, in men and women

TSH/FT_4 tertiles	Differences in total LE	Differences in LE free of CVD	Differences in LE with CVD
TSH tertiles			
Men			
Tertile 1	Reference	Reference	Reference
Tertile 2	1.8	2.1	-0.3
Tertile 3	2.0	1.3	0.7
Women			
Tertile 1	Reference	Reference	Reference
Tertile 2	1.6	1.9	-0.3
Tertile 3	1.7	1.2	0.5
FT_4 tertiles			
Men			
Tertile 1	Reference	Reference	Reference
Tertile 2	-2.1	-1.9	-0.2
Tertile 3	-3.9	-3.1	-0.8
Women			
Tertile 1	Reference	Reference	Reference
Tertile 2	-1.8	-1.7	-0.1
Tertile 3	-3.3	-2.8	-0.5

Data are given as years. Differences in LE are calculated using the first tertile as reference. All life expectancies have been calculated with hazard ratios adjusted for age, cohort, smoking, alcohol intake, education level, marital status, body mass index, systolic blood pressure, total cholesterol, triglycerides, use of antihypertensive medications, use of lipid-lowering medications, prevalent diabetes, and prevalent cancer. Abbreviations: LE, life expectancy; TSH, thyroid-stimulating hormone; FT_4, free thyroxine; CVD, cardiovascular disease.

Supplemental Table 6. LE with and without diabetes at age 50 years among TSH and FT_4 tertiles, in men and women

TSH/FT_4 tertiles	Differences in total LE	Differences in LE free of diabetes	Differences in LE with diabetes
TSH tertiles			
Men			
Tertile 1	Reference	Reference	Reference
Tertile 2	1.3	0.5	0.8
Tertile 3	1.8	1.3	0.5
Women			
Tertile 1	Reference	Reference	Reference
Tertile 2	1.1	0.3	0.8
Tertile 3	1.5	1.1	0.4
FT_4 tertiles			
Men			
Tertile 1	Reference	Reference	Reference
Tertile 2	-1.8	-1.1	-0.7
Tertile 3	-3.6	-2.5	-1.1
Women			
Tertile 1	Reference	Reference	Reference
Tertile 2	-1.5	-0.9	-0.6
Tertile 3	-3.1	-2.0	-1.1

Data are given as years. Differences in LE are calculated using the first tertile as reference. All life expectancies have been calculated with hazard ratios adjusted for age, cohort, smoking, alcohol intake, education level, marital status, body mass index, systolic blood pressure, total cholesterol, triglycerides, use of antihypertensive medications, use of lipid-lowering medications, prevalent cancer, and prevalent cardiovascular disease. Abbreviations: LE, life expectancy; TSH, thyroid-stimulating hormone; FT_4, free thyroxine.

Supplemental Table 7. LE with and without cancer at age 50 years among TSH and FT_4 tertiles, in men and women

TSH/FT_4 tertiles	Differences in total LE	Differences in LE free of cancer	Differences in LE with cancer
TSH tertiles			
Men			
Tertile 1	Reference	Reference	Reference
Tertile 2	1.6	1.3	0.3
Tertile 3	1.6	0.8	0.8
Women			
Tertile 1	Reference	Reference	Reference
Tertile 2	1.4	1.2	0.2
Tertile 3	1.4	0.7	0.7
FT_4 tertiles			
Men			
Tertile 1	Reference	Reference	Reference
Tertile 2	-1.8	-2.1	0.3
Tertile 3	-3.5	-2.7	-0.8
Women			
Tertile 1	Reference	Reference	Reference
Tertile 2	-1.7	-2.0	0.3
Tertile 3	-3.2	-2.6	-0.6

Data are given as years. Differences in LE are calculated using the first tertile as reference. All life expectancies have been calculated with hazard ratios adjusted for age, cohort, smoking, alcohol intake, education level, marital status, body mass index, systolic blood pressure, total cholesterol, triglycerides, use of antihypertensive medications, use of lipid-lowering medications, prevalent diabetes, and prevalent cardiovascular disease. Abbreviations: LE, life expectancy; TSH, thyroid-stimulating hormone; FT_4, free thyroxine.